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ARTERIAL HYPERTENSION AND SECTION OF THE SPLANCHNIC NERVES

DAVID A RYTAND, M D

AND

EMILE HOLMAN, M D

SAN FRANCISCO

The surgical treatment of hypertension, though still in the experimental stage, has been widely reviewed in innumerable reports. In contribution to the literature of an increasing experience with splanchnicectomy, as advocated by Peet, we wish to present the results obtained in 40 patients.

In most of the published series, candidates for operation were selected on more or less arbitrary grounds, for example, most surgeons accept for operation only patients under 50 years of age who are without congestive heart failure, angina pectoris, advanced arteriosclerosis and glomerulonephritis, they further prefer patients whose blood pressure is labile either spontaneously or after the administration of sedatives and vasodilating drugs. However, since the nerve-cutting operations for arterial hypertension are so entirely empiric, we felt justified in ignoring the published contraindications. Hoping to learn more about the effects of operation, we have accepted patients without regard to age, with congestive heart failure, angina pectoris and outright coronary occlusion, hemiplegia or even glomerulonephritis.

The operation in each case consisted of bilateral resection of the greater, the lesser and the least splanchnic nerve through a supra-diaphragmatic approach, together with the resection of, usually, three pairs of lower thoracic ganglions and the intervening chains.

RESULTS

The results of operation may be considered in five categories, as follows:

Group 1—Eight patients (20 per cent) died in from one day to two weeks. This unusually high operative mortality we attribute in part to the fact that at least 6 were patients with far advanced malignant hypertension, who were recognized preoperatively as excessively poor.

From the Departments of Medicine and Surgery, Stanford University School of Medicine

isks On the other hand, 1 of these patients was in comparatively excellent condition but died on the day of operation This patient is of sufficient interest to warrant a brief review of the case

CASE 1—Mrs G, aged 48 years, was known to have had hypertension for ten years She complained of nervousness, fulness in the ears and easy fatigability The

TABLE 1—*Clinical Data Concerning Patients in Group 1*

Name	Age	Duration of Hypertension	Symptoms	Previous Complications	Retinitis	Renal Lesions	Thickened Radial Arteries
Mrs G (case 1 of text)	48	10 yr	Fatigue nervousness fulness in ears	0	±	0	0
Mr M	52	1 yr	Poor vision, headaches, weakness	0	+++	Protein +++ Casts +++ Blood urea 51	
Mr J	49	13 yr	Headaches vomiting	0	+	Protein ++ Casts + Blood urea 51	+
Mrs C	36	½ 10 yr	Poor vision, headaches, vomiting	0	+++	Protein --- Casts + Blood urea 73	0
Mrs F	47	10 yr	Poor vision, headaches, weakness, dyspnea	0	++	Protein +++ Casts + Blood urea 66	++
Mr LeB	47	7 yr	Bloody urine, poor vision	0	++	Gross hematuria	+
Mr McD	49	6 yr	Poor vision fatigue, angina pectoris	Dissecting aneurysm 16 months preoperatively	+++	Protein ++ Casts + Blood urea 69	
Mrs S	57	6 yr	Vertigo, headaches, nervousness	0	0	0	0

fundi oculorum revealed only slight tortuosity of the vessels The radial arteries were soft Roentgen examination showed the heart to be slightly enlarged, and there was a gallop rhythm There were no peripheral signs of heart failure The urine and the concentration of urea in the blood were normal The patient walked into the hospital without difficulty the day before operation, with a blood pressure of 215 systolic and 110 diastolic When she was under anesthesia induced by means of avertin with amylene hydrate, the pressure was 160 systolic and 90 diastolic,

dropping to 80 systolic and 50 diastolic when the second set of splanchnic nerves were cut. At the end of the operation the pressure was 110 systolic and 65 diastolic, and the patient was returned to her room in good condition. Within a few hours she suddenly became comatose, there were disturbances in the respiratory rate, and the blood pressure rose to 205 systolic and 110 diastolic. The coma persisted without localizing signs, and death occurred the next morning, the pulse

(Those Who Died Within Two Weeks After Operation)

Heart	Brain	Blood Pressure				Course
		Before* Operation	Lowest After Operation	Beginning to Rise	Near Preopera- tive Level	
Slightly enlarged, gallop	0	215/110	80/50 1 day	205/110 1 day		Died in one day
		175 220				
		95 120				
Enlarged, pulsus alternans	0	300/140				Died in one day
		225 300+				
		130 190				
0	0	210/140	70/55 1 day	165/105 2 days		Died second day, Cheyne Stokes res- piration, necropsy chronic vascular lesions and edema of midbrain
		160 250				
		90 170				
Gallop, abnormal T waves	0	250/150	95/70 1 day	170/110 3 days		Died third day, coma, temperature 40 C (104 F)
		230 290				
		140 190				
Enlarged	Irrational	240/170	120/70 1 day	160/100 3 days		Died fourth day, irrational high fever, necropsy no cerebral throm- bosis
		235 260				
		150 180				
Gallop	0	240/150	70/40 1 day	200/90 3 days		Died fifth day, bronchopneumonia, necropsy nothing due to operation
Enlarged	Hemiplegia	260/160	100/60 1 day	150/100 2 days	220/140 3 days	Died eleventh day, uremia and bron- chopneumonia necropsy dissecting aneurysm, nothing due to operation
		210 260				
		140 160				
0	Parkinson's disease arterio- sclerosis	240/125	100/80 1 day	160/100 2 days	200/125 2 weeks	Died fifteenth day, streptococcal infection, necropsy nothing but infection due to operation
		240 300				
		120 140				

* In this and in the following tables, the data for blood pressure before operation include average, lowest and highest observations

rate having been about 50, the respiratory rate 70 and the blood pressure 170 systolic and 90 diastolic. Permission for necropsy was not granted.

Four other patients died in the first four postoperative days. Coma and high fever were prominent in their clinical pictures, and 1 had Cheyne-Stokes respiration. Necropsy showed vascular (chronic) lesions

and edema of the midbrain in 1 but nothing at all in another. The 3 other patients died in five to fifteen days of bronchopneumonia.

Outstanding clinical features among this group of 8 patients who died were the high incidences of severe hemorrhagic and exudative retinitis and of renal damage as evidenced by proteinuria, abnormal urinary sediments and increased concentration of urea in the blood. The average blood pressure of these patients was higher (245 systolic and 145 diastolic) than that of almost any other group. These patients could not be separated from those in other groups by any other clinical features, such as age, duration of the disease, thickened radial arteries, previous vascular complications or lability of blood pressure.

Group 2—Eleven patients (27 per cent) died within a year and a half after operation. Half of these were symptomatically relieved for two or three months with particular reference to headache, the others were not benefited. The operation played only a minor role in either hastening or retarding death, which was due to the usual cerebral, cardiac and renal causes. Necropsies of 5 patients failed to show anything striking other than the lesions commonly found in persons with malignant hypertension.

As in group 1, the blood pressure average was extremely high (240 systolic and 155 diastolic) and most of the patients had severe hypertensive retinitis. Renal lesions were less outstanding than among the previous group. Age, duration of the disease and evidences of arteriosclerosis seemed to have nothing to do with the poor results obtained by surgical intervention.

Typical of this group was the patient whose case is reported as follows:

CASE 2—Mr. P., aged 36 years, was known to have had practically normal blood pressure a year before operation. Five months before operation he began to complain bitterly of severe headaches and the blood pressure was found to be 220 systolic and 140 diastolic, he had great visual difficulties and had grown weak. The fundi showed marked arteriovenous nicking, narrow irregular arteriolar lumens and many areas of exudation and hemorrhage, the disks were not elevated. The radial arteries were soft. The heart was only slightly enlarged, and there was no gallop. The urine was entirely normal according to the Addis sediment count, the concentration of urea in the blood was 18 mg. per hundred cubic centimeters. In the two months of observation before operation the blood pressure averaged 210 systolic and 140 diastolic, varying between 170 systolic and 120 diastolic and 250 systolic and 160 diastolic. After operation, the systolic and the diastolic pressures on the first day were 75 and 60 mm. of mercury, respectively, on the second 150 and 100 mm. and by the fourth had reached 220 and 130 mm., respectively. The blood pressure varied around 235 systolic and 145 diastolic for the next two months, after which the patient died of uremia and heart failure. The headaches had been relieved for two or three weeks, but there was severe pain at the site of operation. Necropsy showed the most severe vascular changes

to be in the kidneys (at death there was heavy proteinuria and the concentration of urea in the blood was 321 mg per hundred cubic centimeters, while two months earlier the urine and the concentration of urea in the blood had been normal)

The case history of another of these patients follows

CASE 3—A youth of 17 years had active glomerulonephritis, which began in 1934. There were no clinical signs other than the abnormal urine until April 1937, when he became edematous. He was first seen by Dr T. Addis in July 1937. Examination at that time revealed normal fundi and a normal heart. There were soft radial arteries. The blood pressure was 140 systolic and 100 diastolic. Massive pitting edema was observed. The plasma protein concentration was 3.7 Gm per hundred cubic centimeters, and the blood urea concentration was 60 mg per hundred cubic centimeters. The urine contained 16 Gm of protein per twenty-four hours, and a sediment typical of active glomerulonephritis together with fatty tubular degeneration was observed. There was no great change until November 1937, when the patient suddenly lost much of his vision. Examination showed bilateral severe papilledema and many fresh retinal hemorrhages. There was a gallop rhythm, and the heart was enlarged. The blood pressure was 200 systolic and 150 diastolic. Edema was practically absent. The blood urea content was only 58 mg per hundred cubic centimeters. The urinary findings had not changed.

Because of the absence of renal insufficiency, and since the clinical picture was dominated by the vascular threats to the heart and especially to the eyes brought about by the sudden extreme rise of blood pressure, splanchnic section was considered, and was performed on Nov. 26, 1937. The arterial pressure fell to 130 systolic and 65 diastolic immediately and in the first week varied between 110 systolic and 60 diastolic and 150 systolic and 100 diastolic. However, the temperature rose to 40 C (104 F) on the fourth day, there was oliguria, and the degree of proteinuria decreased, the protein value falling from about 30 Gm per twenty-four hours to 0.5 Gm per twenty-four hours. On the seventh day the patient was anuric. The concentration of urea in the blood rose to 223 mg per hundred cubic centimeters early in the second week, but the blood pressure remained low (110 systolic and 60 diastolic to 160 systolic and 80 diastolic) for three weeks. After a blood transfusion the temperature fell abruptly and diuresis returned, with but 4 Gm of protein in the urine daily. By the fourth week the arterial pressure was 160 systolic and 100 diastolic and by the sixth 220 systolic and 140 diastolic. Vision was improved slightly for a few weeks at this time but relapsed later.

Two months after operation the patient awakened one morning with aphasia. From then until his death two months later, there were miscellaneous neurologic abnormalities, fever, empyema, a rising concentration of urea in the blood and an arterial pressure averaging 210 systolic and 150 diastolic.

Group 3—Nine patients (22.5 per cent) seemed unchanged by the operation, their symptoms were not significantly alleviated, and their blood pressures were not lowered. In this group, too, the symptoms of 4 patients were slightly improved for a month or two, but even then new complaints were substituted for the old. In 1 patient retinal hemorrhages were still present four months after operation, but after nine months they had disappeared although her complaints of poor vision continued, since the operation followed closely a severe clinical exacerbation during which the hemorrhages occurred, and since the arterial

TABLE 2—*Clinical Data Concerning Patients in Group 2 (Those*

Name	Age	Duration of Hyper- tension	Symptoms	Previous Complications	Retinitis	Renal Lesions	Thickened Radial Arteries
Mr P (case 2 of text)	36	5 mo	Headaches, poor vision, weakness	0	+++	Urine normal Blood urea 18	0
Mrs T	34	11 yr	Poor vision headaches	0	+++	Protein + Blood urea 51	±
Mrs H	47	7 yr	Poor vision	0	+++	Urine normal Blood urea 37	0
Miss B	46	7 yr	Headaches	0	+++	Protein + Blood urea 33	
Mrs C	34	7 yr	Headaches	0	++	Urine normal Blood urea 45	++
Mr T	26	? Normal 7 yr ago	Poor vision, hematuria	0	+++	Protein ++ Casts ++ Red blood cells ++ Blood urea 80	
Miss C	23	4 yr	Poor vision, occasional headaches	0	+++	Protein ++ Blood urea 48	
Mr B	48	6 yr	Fatigue	0	±	Urine normal Blood urea 36	++
Miss H	36	2 yr	Headaches	0	++	Urine normal Blood urea 36	
Mr H	52	4 yr	Palpitation, weakness	Glomerulo nephritis for 27 years	++	Protein ++ Casts + Red blood cells ++ Blood urea 57	+
Mr O (case 3 of text)	17	1 mo	Poor vision	Glomerulo nephritis with edema	+++	Protein +++++ Casts +++++ Red blood cells +++ Blood urea 58	0

Who Died Within One and a Half Years After Operation)

Heart	Brain	Blood Pressure				Course
		Before Operation	Lowest After Operation	Beginning to Rise	Near Preopera- tive Level	
Slightly enlarged	0	210/140 170 250 <u>120 160</u>	75/60 1 day	150/100 2 days	220/130 4 days	240/140, 1 mo., 230/150, 2 mo., died after 2 mo., headaches relieved for a while, rapid progression of renal lesion (proteinuria and other find- ings), urea rising to 321 mg per 100 cc, heart failure, necropsy, marked renal vascular lesion
Enlarged, abnormal T wave, left axis deviation	0	235/145 220 250 <u>140 150</u>	90/75 1 day	210/140 3 days	230/160 3 months	Died after 3 mo., with heart failure, uremia and a stroke, headaches better for a month
Enlarged	0	260/180 250 270 <u>165 200</u>	115/100 1 day	150/115 2 days	250/155 1 month	285/140, 4 mo., died after 4 mo., doubtful temporary improvement of vision, suddenly became irrational, coma, 300/210, necropsy arterio- sclerosis of the brain
Enlarged	0	245/150 160 300 <u>110 150</u>	70/55 1 day	205/120 1 week	230/140 2 weeks	Died after 7 mo., headaches better for 4 mo., but severe back pain at operative site
Enlarged	0	260/150 225 240 <u>140 160</u>	120/80 1 day	180/115 1 week	260/170 7 weeks	Died suddenly after 7 mo., 250/150, headaches relieved
Slightly enlarged	0	250/180 235 260 <u>175 185</u>	130/80 1 day	180/125 1 week	220/160 1 month	Died of uremia without relief after 7 mo., 240/160, anemic from hema- turia, epistaxis, melena, necropsy not remarkable except ileitis
Gallop, not enlarged	0	270/180 255 290 <u>175 190</u>	130/80 4 days	200/150 10 days	260/170 2 months	Died without relief after 9 mo. necropsy fresh dissecting aneurysm of aorta
0	0	245/145 230 260 <u>135 155</u>	95/70 1 day	185/115 1 week	230/130 2 weeks	Died of apoplexy without relief after 17 mo., severe back pain at opera- tive site
Gallop	0	235/155 230 245 <u>150 160</u>	90/60 1 day	185/140 1 week	205/125 1 month	Died after 19 mo. of uremia compli- cating a therapeutic abortion, patient married although she quit work because of continuous headaches
Gallop, enlarged	Transient left hemi- plegia	225/155 185 240 <u>120 160</u>	110/85 1 day	150/100 2 days	200/140 4 days	170/120, 1 mo., 180/140, 3 mo., 200/140, 4 mo., 220/160, 7 mo., died after 9 mo. of uremia and heart failure
Gallop, enlarged	0	200/150 200 205 <u>140 160</u>	130/65 1 day 110/60 1 week	160/100 3 weeks	220/140 1½ months	Died after 4 mo., stormy postopera- tive course, fever, anuria, anemia, convulsions, paralyses, aphasia, kidneys no better, vision slightly improved temporarily, necropsy

pressure did not remain appreciably lowered, the operative procedure hardly deserves credit for such a delayed healing

In this group, renal and ocular lesions were less prominent than in those already discussed, although it must be apparent that no sharp

TABLE 3—*Clinical Data Concerning Patients in*

Name	Age	Duration of Hypertension	Symptoms	Previous Complications	Retinitis	Renal Lesions	Thickened Radial Arteries
Mrs C	31	2 mo at least	Poor vision, headaches, dizziness	Convulsion at onset	+++	Protein +--- Casts ++ Blood urea 36	0
Mrs McN	49	3 yr	Headaches, dyspnea, angina pectoris	0	+	Protein + Casts + Blood urea 27	
Mrs G	48	4 yr	Headaches, "bursting" sensation	Hysteria paroxysmal tachycardia	0	Urine normal Blood urea 20	0
Mr L	29	3 yr	Heart failure	0	+	Protein +--- Casts ++ Blood urea 46	++
Mr K	40	6 yr	Headaches nervousness fits of anger	Anemia	0	Protein ++ Casts + Blood urea 40	+
Mrs N	40	17 yr	Fatigue, dizziness	0	±	Urine normal Blood urea 15	0
Dr McK	51	16 yr	None	Hemiplegia 9 months	0	Urine normal Blood urea 21	±
Mrs S	35	7 yr	Poor vision, headaches, epistaxis	0	+++	Protein + Blood urea 34	0
Mr J	40	3 yr	Headaches	0	0	Normal	0

lines can be drawn. The average blood pressure was lower (200 systolic and 130 diastolic). There were no outstanding clinical features.

Group 4—Six patients (15 per cent) enjoyed appreciable alleviation of symptoms six to forty-eight months after operation, although their pressure levels were unaltered. In 1 of these patients, headaches

disappeared and a previous hemorrhage into the vitreous humor clarified enough to permit improved vision eight months after operation, although at the fifth postoperative month the patient had not been improved. In the case of the second patient, angina pectoris and dyspnea on effort

Group 3 (Those Unchanged After Operation)

Heart	Brain	Blood Pressure				Course
		Before Operation	Lowest After Operation	Beginning to Rise	Near Preopera- tive Level	
Not enlarged, abnormal T waves	(Previous convulsion) 0	195/125	90/60 1 day	150/100 2 days	180/140 1 week	150/95, 1 mo, 190/115, 2 mo, 190/130, 3 mo, fundi and vision not im- proved, headaches same, 185/120, 4 mo, 190/130, 10 mo, vision same, fundi improved, kidneys unchanged
		180 215				
		115 140				
Not enlarged, left axis deviation	0	160/90	90/60 1 day	130/80 2 weeks	180/110 2 months	210/130 after 6 mo, headaches better but legs tire and in general no better
		140 220				
		90 110				
0	0	215/125	95/70 1 day	120/80 2 weeks	220/120 15 months	"Bursting" sensation better for about 6 mo, but patient confined to bed
		170 220				
		100 130				
Moderate heart failure	0	220/160	110/75 1 day	195/150 3 days	200/150 1 month	215/125, 2 mo, feels better, 220/150 and heart failure at 1 yr, kidneys unchanged
		210 230				
		150 175				
0	0	200/140	85/60 1 day	180/120 2 days	220/130 2 weeks	235/140 at 2 mo, headaches same
		160 230				
		100 140				
Gallop, abnormal T waves	0	210/130	120/95 1 day	180/115 1 week	200/140 2 weeks	230/130 at 20 mo, heart failure, indigestion with scant evidence of disturbed gastric motility soon after operation
		200 220				
		120 140				
0	Residuals of right hemiplegia	225/130	100/70 1 day	160/100 1 week	190/120 2 weeks	140/100, 1 mo, 200/120, 2 mo con- vulsions 8 mo postoperatively second cerebral vascular accident 33 mo, blood pressure 190/90
		210				
		115				
Gallop, left axis deviation	0	250/150	115/80 1 day	150/100 2 days	200/145 4 days	270/150 after 1 mo, vision and head- aches only slightly improved
		210 275				
		130 160				
0	0	170/100	100/60 1 day	170/110 5 days	170/90 2 weeks	170/90, 1 mo, headaches same 170/95, 2 mo, headaches same 180/105, 3 mo, headaches same
		165 220				
		95 110				

disappeared, vision improved and she felt herself to be in splendid condition, but edema appeared and digitalis was prescribed. A third patient was relieved of the sensation of pounding in the vessels. A fourth, hysterical before operation, was calmer and had fewer headaches, she was less easily fatigued. The fifth was somewhat relieved of pound-

ing vessels, fulness in the head and great lassitude, while they were partially relieved, the degree of these symptoms clearly fluctuated with the patient's economic and psychic state

As a group, these patients had no outstanding clinical features, they in general resembled the patients of group 3, described in the preceding section

TABLE 4—*Clinical Data Concerning Patients in Group 4 (Those Whose Blood*

Name	Age	Duration of Hypertension	Symptoms	Previous Complications	Retinitis	Renal Lesions	Thickened Radial Arteries
Mr B (case 4 of text)	38	10 yr	Pounding vessels, fulness in head	Hemiplegia 6 mo preoperatively, glomerulonephritis ?	0	Protein ++ Casts + Red blood cells ++ Blood urea 60	0
Mrs W	44	5 yr	Headache, fatigue	Hysteria	0	Urine normal Blood urea 25	0
Miss N	33	7 yr	Fatigue, pounding, fulness in head	Deafness	0	Urine normal Blood urea 23	0
Mr S	45	2 yr	Poor vision, headaches, vomiting	Obesity	++++ Vitreous hemorrhage	Protein + Casts + Blood urea 53	0
Mrs C	52	4 yr	Angina pectoris	0	++	Protein + Blood urea 24	+
Mr M	28	1 yr	Headaches	0	+	Protein + Blood urea 48	0

The case of 1 of these patients is summarized as follows

CASE 4—Mr B, aged 38 years, was known to have had albuminuria and hypertension for ten years. During that time he complained of inability to work because of fulness in the head and consciousness of markedly pulsating arteries. Six months before operation there was an attack of right hemiplegia, which cleared except for slight weakness. On examination the patient appeared well. The fundi and the heart were normal. The radial arteries were soft. There were no abnormal neurologic signs. The urine contained a moderate amount of protein and increased numbers of red blood cells, casts and renal epithelial and white blood cells. The concentration of urea in the blood was 60 mg per hundred cubic centimeters.

Although the patient had had hemiplegia and probably had glomerulonephritis, the arterial pressure was variable. It averaged 180 systolic and 125 diastolic and was as high as 205 systolic and 140 diastolic, but on the day before section of the splanchnic nerves (April 26, 1935) it was actually normal (135 systolic and 85 diastolic). On the first and the second postoperative day the pressure was 95 systolic and 70 diastolic and 140 systolic and 100 diastolic, respectively, after four months it had reached the preoperative level, 200 systolic and 125 diastolic.

Pressure Was Unchanged But Whose Symptoms Were Alleviated After Operation)

Heart	Brain	Blood Pressure				Course
		Before Operation	Lowest After Operation	Beginning to Rise	Near Preoperative Level	
0	Previous hemiplegia	180/125	95/70 1 day	140/100 2 days	200/125 4 months	175/135 after 17 mo, feels fine, no pounding, 190/120 after 21 mo, 200/145 after 30 mo, gout, kidneys unchanged, 170/120 after 45 mo
		135 205				
		85 140				
0	0	200/135	120/80 1 week	145/95 2 weeks	220/110 6 months	235/130 after 9 13 mo, 220/120 after 17 23 mo, 240/130 after 29 mo, much better as to headache, but still tires easily
		135 250				
		95 160				
0	0	190/135	125/90 1 week	170/125 2 months	200/140 12 months	210/150 after 34 mo, 190/130 after 38 mo, 200/150 after 47 mo, able to work but tires easily, symptoms vary great deal, severe pain in back at operative site
		170 225				
		110 150				
0	0	190/130	90/60 1 day	160/100 2 days	190/120 1 week	180/125 after 5 mo, vision no better, headaches, 180/120 after 8 mo, vision and headaches better
		175 210				
		115 140				
Angina pectoris, auricular fibrillation, heart failure (mild)	0	225/140	100/50 1 day	175/125 4 days	200/125 1 week	205/135 after 13 mo, no pain or dyspnea, 220/120 after 5 mo, vision improved, 240/140 after 6 mo, no complaint, but edema present, 235/135 after 8 mo, digitalis
		200 250				
		110 160				
Slightly enlarged, left axis deviation, abnormal T waves	0	205/145	90/60 1 day	180/120 3 days	210/150 1 week	180/130 after 2 wk, 220/155 after 20 mo, headaches relieved, no new retinitis
		200 210				
		140 150				

Two and a half and four years after operation the arterial pressure was 200 systolic and 145 diastolic and 170 systolic and 120 diastolic respectively. Thus, in spite of the extremely labile pressure, operation failed to induce a reduction. However, the symptoms of arterial pounding vanished with operation and have not returned. The patient has been able to resume his work as a rancher. The renal lesion has not altered in intensity or extent.

Group 5—It was in a group of 6 patients (15 per cent) that the best results followed operation, their average arterial pressure falling from 200 systolic and 120 diastolic to 155 systolic and 100 diastolic. They ranged in age from 30 to 54 years (average 39 years) and were

known to have been hypertensive for from two to ten years. None of these patients had any urinary abnormalities or elevated blood urea concentration, and all but 1 had perfectly normal fundi. All had thickened radial arteries. One had survived an attack of coronary occlusion, and 2 presented themselves with congestive heart failure. Since opinions of the value of section of the splanchnic nerves depend largely on the critical study of these patients, their histories are presented.

CASE 5—Mr. Y, aged 30 years, had had known hypertension for eighteen months when he was rejected after an examination for life insurance. Six months

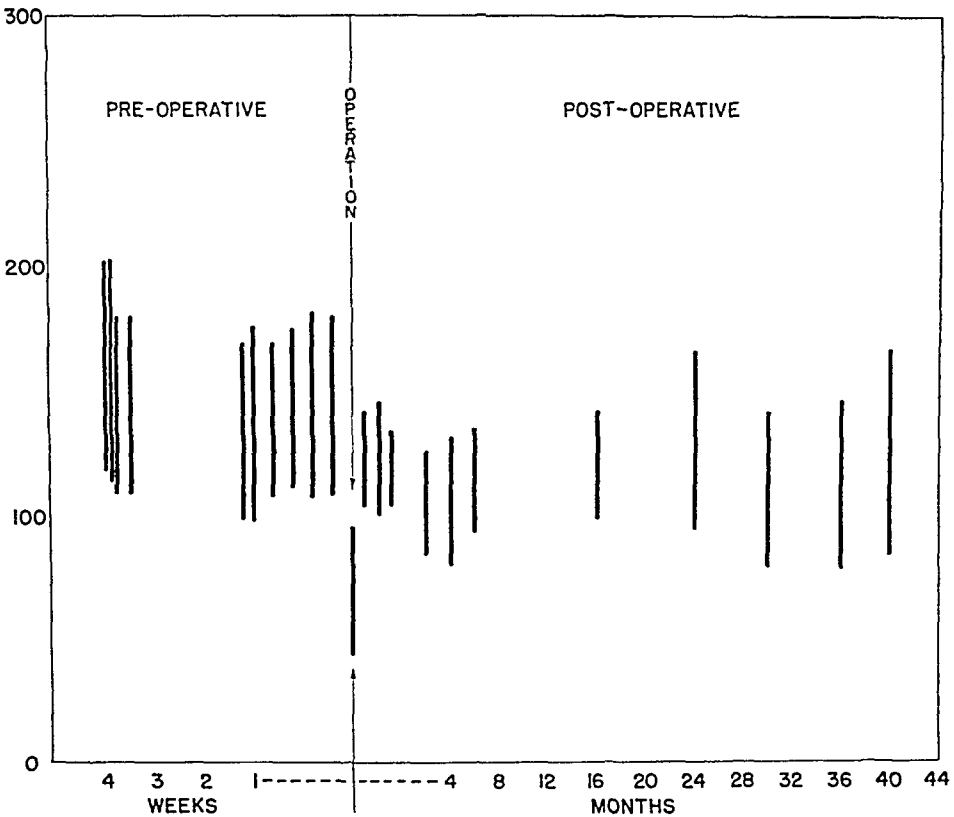


Chart 1—Arterial pressure record of Mr. Y (case 5)

before operation he began to complain of moderately severe headaches, often associated with short attacks of palpitation and tachycardia which started and stopped abruptly. On examination he appeared to be well. The fundi were normal. The heart was normal. The radial arteries seemed slightly thickened. On the first day of observation the arterial pressure was 180 systolic and 120 diastolic, falling to 160 systolic and 110 diastolic on the same day, thereafter it averaged 155 systolic and 110 diastolic and was on occasion as low as 150 systolic and 100 diastolic. The urine was entirely normal according to the Addis sediment count. The concentration of urea in the blood was 33 mg per hundred cubic centimeters. An electrocardiogram showed only left axis deviation. Section of the splanchnic nerves was performed on May 30, 1936. Figure 1 gives the record of the arterial pressure. The headaches and palpitation have been absent

since operation The pressure remained lower for three years after operation, although it was near the preoperative level on several occasions, after forty months the blood pressure was 165 systolic and 105 diastolic

CASE 6—Mrs P, aged 31 years, had a ruptured tubal pregnancy two years before section of the splanchnic nerves Shortly thereafter she suffered severe headaches, for which a physician was consulted, hypertension was found Because the headaches persisted in spite of medical treatment and because the patient was growing short of breath on effort, she was considered a subject for operation She appeared perfectly well The fundi showed practically no vascular changes and no exudate or hemorrhage The radial arteries were firm and the heart was slightly enlarged The urine sediment count was completely normal, and the

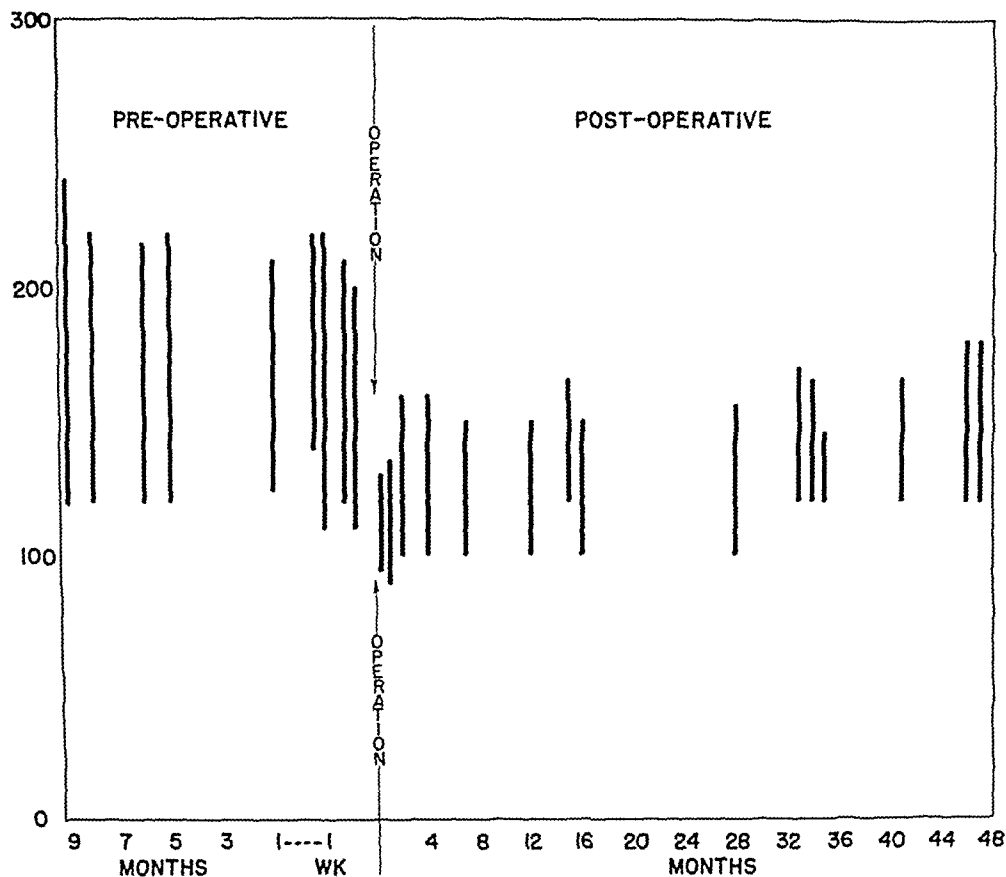


Chart 2—Arterial pressure record of Mrs P (case 6)

concentration of urea in the blood was only 27 mg per hundred cubic centimeters An electrocardiogram gave normal readings The operation was performed on June 22, 1935 Figure 2 gives the record of the arterial pressure The pressure level fell from a preoperative average of 215 systolic and 120 diastolic to 155 systolic and 100 diastolic for the first year, but between the third and the fourth year it had risen to 180 systolic and 120 diastolic The diastolic pressure, therefore, was not significantly reduced However, the headaches and exertional dyspnea disappeared immediately after the operation and have not returned four years afterward

CASE 7—Mr McK, aged 45 years, was found to be hypertensive nine years before the splanchnic nerve section, performed on May 11, 1937 The hypertension was discovered in the course of an examination for bronchial asthma Five years before the operation he suffered his first and only symptom of hypertension,

namely, blurred vision because of a hemorrhage in the left retina. When he was first examined here by Dr T. Addis in 1933 he was an obese, highly strung man with mild bronchial asthma. The left fundus oculi showed scarring from the hemorrhage eight months earlier, while the right showed arteriosclerosis without hemorrhage or exudate, visual acuity was good. Roentgen examination showed that the heart was not enlarged. The radial arteries were firm. An electrocardiogram showed T to be inverted in the first and the second lead. The urine sediment count was entirely normal and the concentration of urea in the blood was 32 mg per hundred cubic centimeters.

With medical management the arterial pressure soon fell from 180 systolic and 110 diastolic to normal levels, but shortly increased again. In the four years

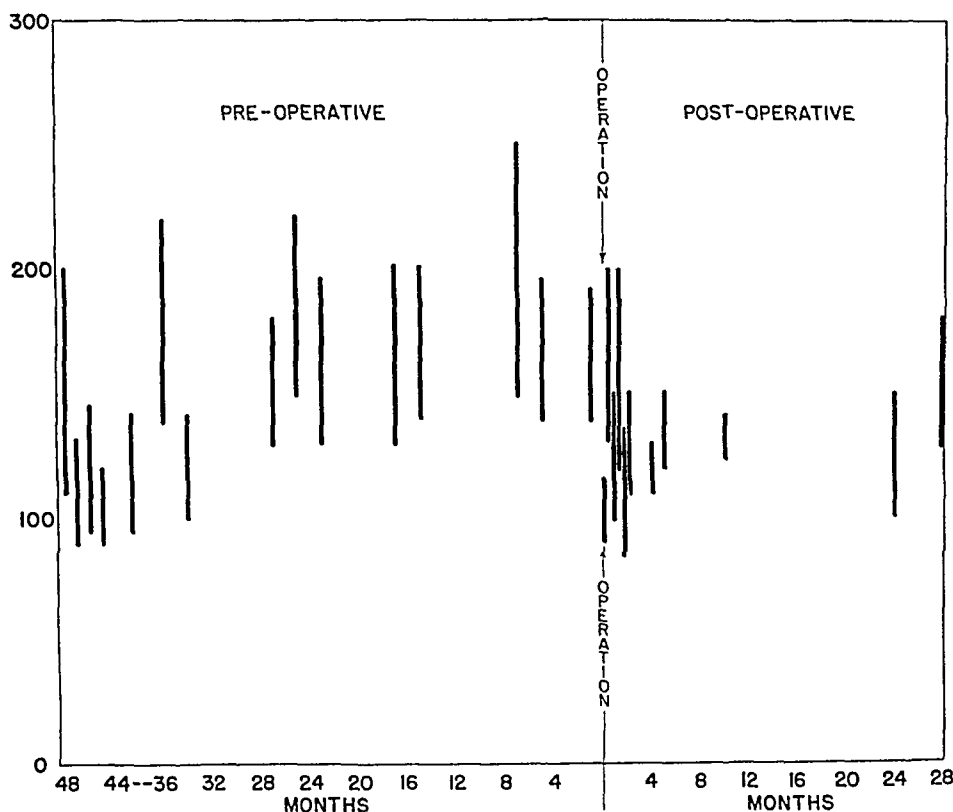


Chart 3—Arterial pressure record of Mr McK (case 7)

of preoperative observation the average yearly systolic and diastolic blood pressure increased from 145 and 95 mm of mercury, respectively, to 170 and 115 mm, 205 and 140 mm and 220 and 145 mm, respectively. The general physical condition remained unchanged until seven months before operation, when there appeared fresh hemorrhages in the right retina. Two months before operation another hemorrhage occurred, this time in the left retina. The roentgen examination showed an increase in fulness of the aorta, while in the electrocardiogram T had become upright in the second lead. The urine and the concentration of urea in the blood remained normal. Section of the splanchnic nerves was done, because of the threat to the vision, on May 11, 1937. Figure 3 gives the pressure record.

A month after operation there were still fresh hemorrhages to be seen in the left fundus. The vision has improved about as it did spontaneously after the first retinal hemorrhage. The patient having reported "I never felt better in my life"

just before the operation, his general condition remained unchanged (except for temporary weakness and backache after operation) The arterial pressure response showed a great fall in systolic level, a smaller change in diastolic level and for a time a small pulse pressure although he was clinically well One should note the levels of 200 systolic and 130 diastolic and of 200 systolic and 120 diastolic on the second and the sixth postoperative day, when there was transient fever Twenty-eight months postoperatively the blood pressure was 180 systolic and 130 diastolic and the patient felt completely well There were no retinal hemorrhages, and only 1 retinal artery appeared at all abnormal

CASE 8—Mrs M, a nurse aged 37 years, had been kept in bed for six weeks because of "heart trouble" (cyanosis) following a pregnancy fifteen years before

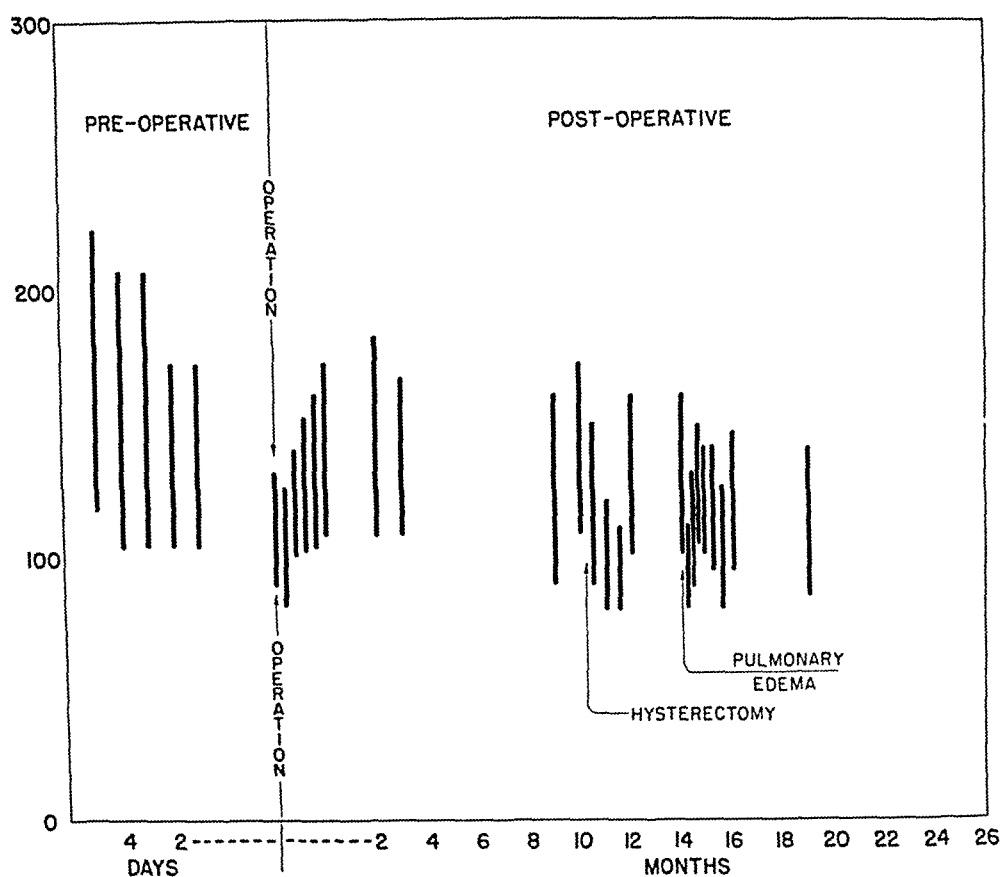


Chart 4—Arterial pressure record of Mrs M (case 8)

section of the splanchnic nerves She was then well for eight years, when dyspnea and palpitation on effort appeared Five years before operation she noted edema of the ankles, the dyspnea became worse and once there was an episode resembling acute pulmonary edema Rest and the administration of digitalis, a theobromine-phenobarbital preparation, and barbitol gave some relief Two years before operation the systolic pressure was reported to have been 170 to 220 mg of mercury, and in addition the patient complained of dizziness, headaches, weakness nervousness and visual disturbances Later she had an almost constant dull precordial pain radiating down the left arm, made worse by effort She was seen by us for the first time only four days before section of the splanchnic nerves, performed on April 14, 1938 On examination she appeared perfectly well, in striking contrast to her previous condition The fundi showed narrow arterioles but no exudate or hemorrhage The neck veins were not distended, and the lungs

were clear. In the roentgenogram the shadow of the root of the aorta was widened but the heart was not enlarged. The heart sounds were normal. The radial arteries were somewhat thickened. The liver was not palpable, and there was no edema. There was a fibromyomatous uterus. The urinary sediment count was normal, and the blood urea concentration was 25 mg per hundred cubic centimeters. An electrocardiogram showed prolonged conduction time (digitalis) and left axis deviation.

The arterial pressure, 220 systolic and 120 diastolic on admission, fell to 170 systolic and 105 diastolic in only four days, when section of the splanchnic nerves was done. Figure 4 shows the pressure records.

Three months after operation the headaches were fewer but all other symptoms persisted (perhaps slightly better, although edema occasionally extended halfway to the knees). By the ninth postoperative month the patient felt much improved but had paresthesias of the legs and precordium. An episode of excessive exertion three months earlier had precipitated severe dyspnea for two days, but other than that there had been no breathlessness.

Eleven months after the section of the splanchnic nerves a hysterectomy was done. When the patient was in the operating room under the influence of sedative drugs awaiting this operation, the pressure was 160 systolic and 100 diastolic, just as it had been in similar circumstances almost a year earlier. On the tenth day after hysterectomy the pressure was only 120 systolic and 80 diastolic (170 systolic and 110 diastolic on the tenth day after splanchnic nerve section), and the patient was dismissed from the hospital. The pressure returned to 160 systolic and 100 diastolic when she was at home, where walking up a flight of stairs induced dyspnea. Twinges of substernal pain occurred.

Three months after hysterectomy there was an attack of rather severe substernal pain, with great breathlessness and frothy, pink sputum, the patient's physician heard many rales and found the arterial pressure to be 160 systolic and 100 diastolic. She was sent to bed, irrational because of sedatives, with a pressure of 110 systolic and 80 diastolic to 150 systolic and 105 diastolic. An electrocardiogram showed no changes which might be interpreted as those of myocardial infarction. The urine and the concentration of urea in the blood remained normal and the fundi unchanged. Roentgen examination showed that the heart had not enlarged. When last seen, eight months after hysterectomy, the patient felt well and had been hunting deer, the blood pressure was 140 systolic and 85 diastolic.

CASE 9—Mr. L., a man aged 54 years, was known to have had hypertension for seven years prior to the section of the splanchnic nerves. He had come under observation because of angina pectoris and frequent exacerbations of a chronic infection of the urinary tract. When first seen by Dr. A. L. Bloomfield, in 1934, he was ill with hyperthyroidism, subtotal thyroidectomy was done elsewhere in March 1934. In June 1934 he suffered in rapid succession a classic attack of myocardial infarction, a flare-up of the infection of the urinary tract and a recurrence of hyperthyroidism. After heavy doses of roentgen rays had failed to induce a remission in the hyperthyroidism, he was given iodine and a second thyroidectomy was done in September 1934, after which there had been no recurrence. By December 1934 the heart was enlarged and pulsus alternans and a gallop rhythm were present. Glyceryl trinitrate was fairly effective in controlling the angina, and digitalis was given. At this time the patient retired from his exacting duties as newspaper editor.

During 1935 he suffered attacks of flushing and pain in the chest severe enough to cause him to weep, in these episodes the pulse became rapid and the arterial pressure rose from about 180 systolic and 130 diastolic to as high as 245 systolic

and 185 diastolic. These attacks, induced by emotion and arising spontaneously, resembled the syndrome described by Page¹ as diencephalic in origin. By March of 1936 the patient was completely incapacitated, taking as many as twenty tablets of glyceryl trinitrate during a day at rest in bed, he had a large heart, pulsus alternans, a gallop rhythm, a palpable liver and a trace of edema. The fundi revealed no exudate or hemorrhage. The radial arteries were slightly thickened. Except for a few white blood cells the urine was normal, and the blood urea concentration was 34 mg per hundred cubic centimeters. Section of the splanchnic nerves was performed on April 13, 1936. Figure 5 gives the blood pressure readings.

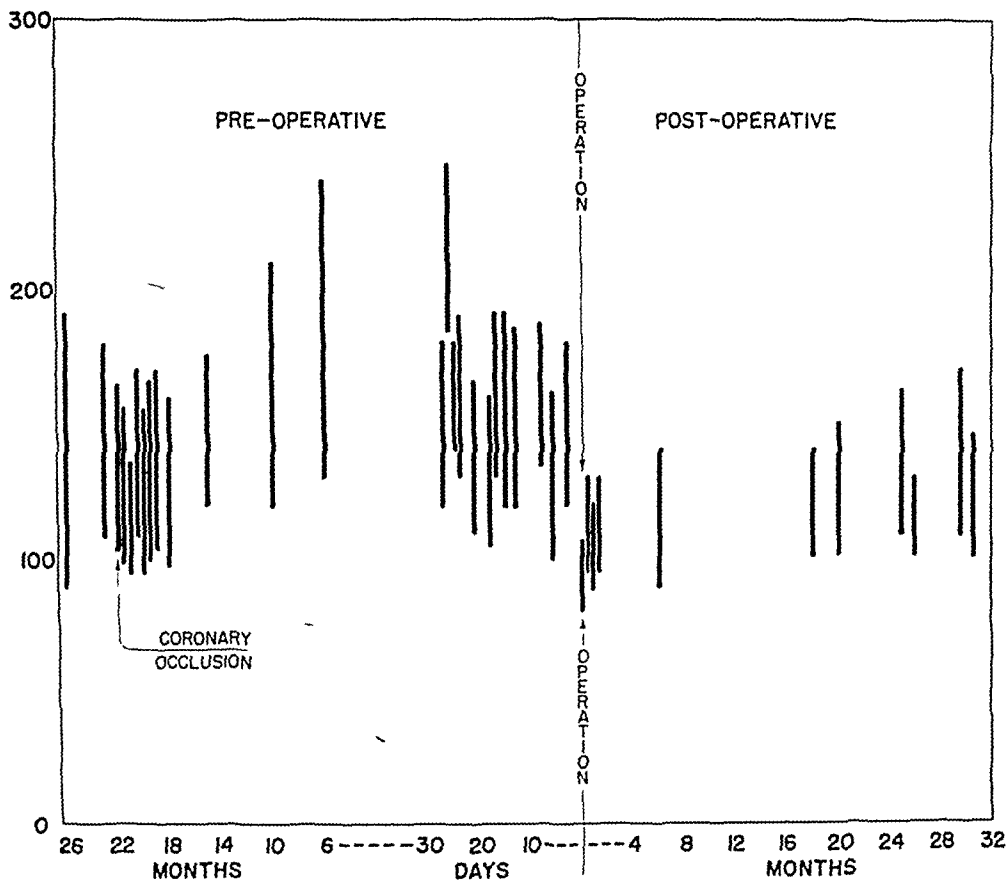


Chart 5—Arterial pressure record of Mr L (case 9)

It is of some interest that the fall in arterial pressure after the section of the splanchnic nerves was comparable in degree to that after the earlier myocardial infarction but was more prolonged. There have been no more "diencephalic" attacks, but the angina pectoris and congestive heart failure persist in moderate degree. The heart is larger now than ever.

CASE 10—G, an unmarried woman aged 38 years, had been hypertensive for ten years, the discovery was made by a physician whom she consulted for fatigability. Eight years before section of the splanchnic nerves the arterial pressure was reported to have been 250 systolic and 125 diastolic, but there were no complaints other than great lassitude until February 1935, when she collapsed while climbing stairs. Dr Malcolm Jones attended her at that time, he found

1 Page, I H. A Syndrome Simulating Diencephalic Stimulation Occurring in Patients with Essential Hypertension, *Am J M Sc* 190 9-14 (July) 1935

hypertensive cardiac disease with failure (dyspnea and edema) and a blood pressure of 250 systolic and 135 diastolic. During rest in bed for seven months, she improved and the pressure fell to 200 systolic and 100 diastolic. It promptly returned to 250 systolic and 120 diastolic on resumption of activity, and two months later she again became dyspneic. Just before the section of the splanchnic nerves on Nov 28, 1935, examination showed the patient to be thin, weak and dyspneic on the slightest effort. The fundi were normal. The heart was greatly enlarged. The liver was palpable, and there was edema of the ankles. The radial arteries were slightly thickened. The urine was entirely normal, and the blood contained 33 mg of urea per hundred cubic centimeters. The arterial pressure

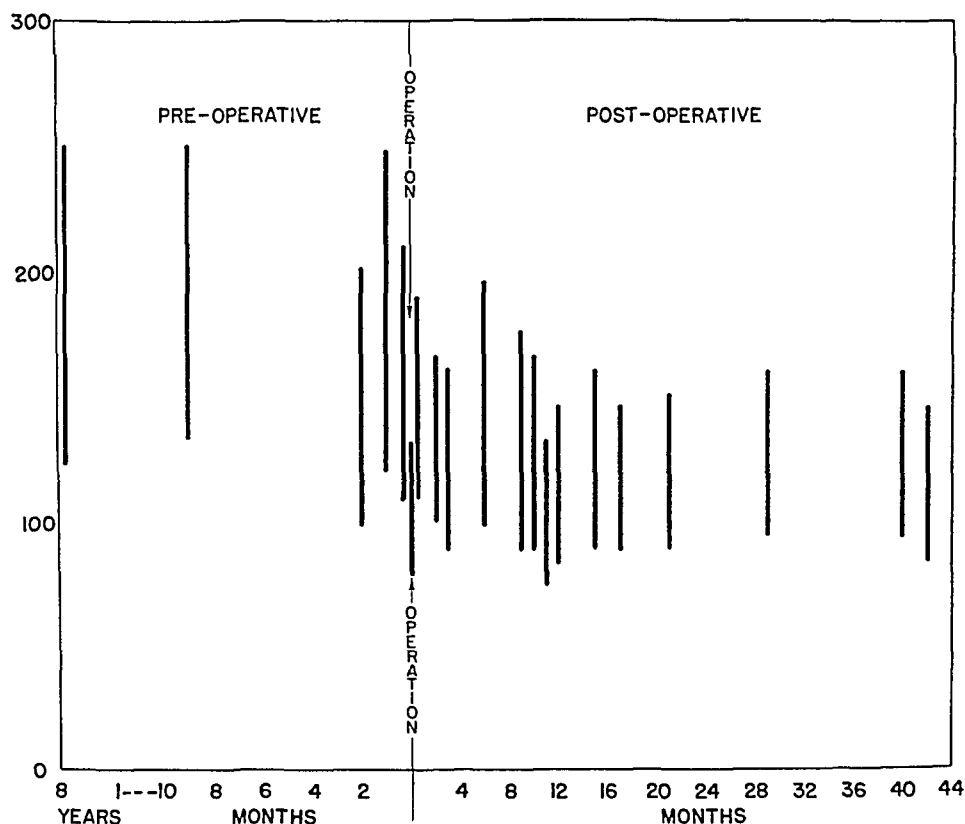


Chart 6—Arterial pressure record of Miss G (case 10)

was 240 systolic and 120 diastolic, dropping to 195 systolic and 110 diastolic after three days of rest in bed. Figure 6 gives the blood pressure records.

On the day following operation the pressure was 130 systolic and 80 diastolic but rose to 180 systolic and 110 diastolic after one week. After another week it was 190 systolic and 110 diastolic and as late as six months after operation it was once 195 systolic and 100 diastolic. However, a year after operation it was as low as 130 systolic and 75 diastolic and since then has averaged 150 systolic and 90 diastolic. The last examination, three and a half years after operation, showed the pressure to be only 145 systolic and 85 diastolic.

The symptoms and signs of heart failure rapidly disappeared. As early as three months postoperatively the heart was reported as normal in size. A year after operation the patient married. She now complains of fatigue and dyspnea only if she works hard but feels better while taking 0.1 Gm of digitalis daily. There is no edema.

The results in this case are among the best achieved in the present series. It is odd, however, that while the symptomatic improvement appeared at once, the main decline in arterial pressure did not occur until six months after operation.

COMMENT

Before discussing the results of operation it might be profitable briefly to review the pathologic physiology of arterial hypertension, with special reference to denervation of the splanchnic vessels.

The arterial pressure varies directly with either of two factors, cardiac output and peripheral resistance. Under various physiologic conditions during health, these two factors usually vary inversely, minimizing fluctuations in pressure. It is now accepted, however, that in patients with arterial hypertension resistance to blood flow is increased in the presence of a normal cardiac output. Furthermore, it is known that the site of such an increased resistance is not in the large vessels but in vessels of the order of size of arterioles,² that the increased resistance is not confined to the splanchnic region but is widespread,³ and that under certain conditions even chronically increased resistance may fall abruptly.⁴ When hypertension is of short duration, as in persons with acute nephritis, there is evidence that the arteriolar lumens may relax fully to normal size under the appropriate stimuli,⁵ but when hypertension is chronic such relaxation is not complete in short experiments,³ however, even after arterial hypertension has persisted for long periods in dogs with one renal artery partially constricted, removal of the kidney abolishes the hypertension and hence must permit the arterioles to regain normal size. The clinically important analogue of this, namely the condition of patients with unilateral pyelonephritis or renal anomalies, has already been described.⁶

The proponents of denervating operations hope to help their patients by bringing about a local region of normal resistance in the splanchnic

2 Oppenheimer, E. T., and Prinzmetal, M. Role of the Arteries in the Peripheral Resistance of Hypertension and Related States, *Arch. Int. Med.* **60**: 772-782 (Nov.) 1937.

3 Pickering, G. W. Peripheral Resistance in Persistent Arterial Hypertension, *Clin. Sc.* **2**: 209-235 (May) 1936.

4 Prinzmetal, M., and Wilson, C. The Nature of the Peripheral Resistance in Arterial Hypertension, with Special Reference to the Vasomotor System, *J. Clin. Investigation* **15**: 63-83 (Jan.) 1936.

5 Pickering, G. W. Observations on the Mechanism of Arterial Hypertension in Acute Nephritis, *Clin. Sc.* **2**: 363-372 (Dec.) 1936.

6 (a) Leadbetter, W. F., and Burkland, C. E. Hypertension in Unilateral Renal Disease, *J. Urol.* **39**: 611-626 (May) 1938. (b) Weiss, S., and Parker, F., Jr. Pyelonephritis: Its Relation to Vascular Lesions and to Arterial Hypertension, *Medicine* **18**: 221-316 (Sept.) 1939.

bed, ignoring the fact that only widespread changes of resistance alter blood pressure appreciably, while local changes of resistance, as in cases of arteriovenous fistula or severe peripheral arteriosclerosis, predominantly, affect blood flow. Moreover, they have neglected those investigations which point out that denervated vessels shortly regain their original tone even when regeneration of nerves does not occur, apparently sensitized to a substance circulating in the blood.⁷

In addition it has been asserted that section of splanchnic nerves (largely by denervating the adrenal glands) prevents sharp rises of pressure under emotion and exertion. Even our patients in whose cases the best results appeared, however, exhibited marked fluctuation of pressure both soon and late after operation, we were not able to demonstrate a decreased response to the Hines-Brown cold test⁸ after operation. In the case of 1 patient "diencephalic" attacks have not been observed since operation. Although his angina pectoris persists, the blood pressure has not been recorded during the pain.

Finally, on the assumption that the pathogenesis of essential hypertension is similar to that of the arterial hypertension in animals with partially occluded renal arteries, it has been hoped that section of the splanchnic nerves would permit an increased renal blood flow by means of denervation of the kidneys, thereby stopping the formation of the substance⁹ which causes hypertension in the Goldblatt dog.

It has been claimed that the ischemic kidney of the Goldblatt dog has its clinical counterpart in human kidneys (1) with ischemia contracted secondarily to chronic renal disease, especially when the ischemia is unilateral,¹⁰ (2) with partially occluded renal arteries¹¹ and (3) associated with coarctation of the aorta.¹² That evidence which favors the identity of essential hypertension and the hypertension of the Goldblatt animal is less direct and more confused. In each condition, the renal tissue may appear normal under the microscope, the urine is normal and the usual clinical tests of renal function may give normal results.

7 Cannon, W. B. Factors Affecting Vascular Tone, *Am Heart J* **14** 383-398 (Oct) 1937

8 Hines, E. A., Jr., and Brown, G. E. A Standard Test for Measuring the Variability of Blood Pressure. Its Significance as an Index of the Prehypertensive State, *Ann Int Med* **7** 209-217 (Aug) 1933

9 Blalock, A., and Levy, S. E. Studies on the Etiology of Renal Hypertension, *Ann Surg* **106** 826-847 (Nov) 1937

10 Butler, A. M. Chronic Pyelonephritis and Arterial Hypertension, *J Clin Investigation* **16** 889-897 (Nov) 1937

11 Blackman, S. S., Jr. Arteriosclerosis and Partial Obstruction of the Main Renal Arteries in Association with "Essential" Hypertension in Man, *Bull Johns Hopkins Hosp* **65** 353-375 (Nov) 1939

12 Rytand, D. A. The Renal Factor in Arterial Hypertension with Coarctation of the Aorta, *J Clin Investigation* **17** 391-399 (July) 1938

The data¹³ which seem to indicate that renal blood flow is reduced in persons with essential hypertension may, in view of more recent studies,¹⁴ have to be interpreted as meaning that in hypertensive patients the maximal possible renal flow is less than in normal people, such a finding would be expected because of renal arteriosclerosis and could by no means be interpreted as evidence of renal ischemia which had caused hypertension. The role of renal ischemia in elevating arterial pressure even in the Goldblatt dog is not clear, for hypertension may be present in association with normal renal blood flow¹⁵. In contrast to other pressor substances the pressor extract, renin, obtained from normal kidneys raises arterial pressure without redistributing peripheral blood flow,¹⁶ as in patients with hypertension, while it has been shown fairly definitely that the kidney beyond a Goldblatt clamp contains more renin than a normal kidney,¹⁷ the evidence is not so satisfactory that the kidneys of patients who die of hypertension have more renin than do those of nonhypertensive controls¹⁸.

In the presence of an actual obstruction in a renal artery or the aorta, as in the Goldblatt dog and in a few patients, nerve-cutting operations cannot elevate renal blood flow and can be of no value¹⁹. The contradictory results after renal denervation, section of splanchnic nerves, anterior rhizotomy or even complete sympathectomy in animals with other types of experimental hypertension (produced by such means as cisternal injections of kaolin, carotid sinus denervation, oxalate or antiserum "nephritis" and renal venous stasis) cannot at present be

13 Smith, H. W. Studies in the Physiology of the Kidney, Porter Lectures, Series 9, Extension Division, University of Kansas, Lawrence, Kan., 1939.

14 Chesley, L. C., and Chesley, E. R. The Diodrast Clearance and Renal Blood Flow in Normal Pregnant and Non-Pregnant Women, *Am J Physiol* **127**:731-737 (Nov.) 1939.

15 Enger, R., Linder, F., and Sarie, H. Die Wirkung quantitativ abgestufter Drosselung der Nierendurchblutung auf den Blutdruck, *Ztschr f d ges exper Med* **104**:1-9, 1938.

16 Landis, E. M., Montgomery, H., and Sparkman, D. The Effects of Pressor Drugs and of Saline Kidney Extracts on Blood Pressure and Skin Temperature, *J Clin Investigation* **17**:189-206 (March) 1938.

17 Harrison, T. R., Blalock, A., Mason, M. F., and Williams, J. R., Jr. Relation of Kidneys to Blood Pressure. Effects of Extracts of Kidneys of Normal Dogs and of Dogs with Renal Hypertension on Blood Pressure of Rats, *Arch Int Med* **60**:1058-1068 (Dec.) 1937.

18 Prinzmetal, M., Friedman, B., and Abramson, D. I. The Nature of Arterial Hypertension with Special Reference to the Role of the Kidney, *Ann Int Med* **12**:1604-1616 (April) 1939.

19 Goldblatt, M. Experimental Hypertension Induced by Renal Ischemia, in *Harvey Lectures* (1937), Baltimore, Williams & Wilkins Company, 1938 vol 33, p 237.

transferred to patients with essential hypertension²⁰ Moreover, it is difficult to elevate renal blood flow above normal for any length of time by actual denervation²¹

If section of the splanchnic nerves fails to alter peripheral resistance either directly or by means of action through the kidneys (we have not observed the reported²² improvement in renal function) it might conceivably lower arterial pressure by a reduction of cardiac output In our patients in whose cases the best results were achieved, the fall of pulse pressure, with relatively little change in diastolic level but with great reduction of systolic pressure, was striking It is known that other operations cause a reduction of cardiac output by 40 per cent for two or three days,²³ but apparently no one has studied cardiac output after section of the splanchnic nerves The early great fall in blood pressure observed in all our patients is probably due to this mechanism Since this function is normal in persons with hypertension, it is highly unlikely that operation would cause a prolonged subnormal level of cardiac output

The prognosis of any given hypertensive patient is well known to be uncertain Barring the development of congestive heart failure or sudden occlusion of arteriosclerotic cerebral or cardiac arteries, the prognosis depends in general on a relatively minor factor, the height of the pressure, and on a major one, the extent of vascular lesions, which when present in a high degree lead to the diagnosis of malignant hypertension In two regions these lesions give clear evidence of their presence in the eyes as hypertensive retinitis, such as irregular arterial lumens, arteriovenous nicking, hemorrhage, exudate and papilledema, and in the kidneys as arteriosclerotic Bright's disease (nephrosclerosis) associated with proteinuria, cylinduria, increased rates of excretion of tubular epithelial cells and red blood cells, occasional gross hematuria and decreased renal function

20 (a) Braun, L, and Samet, B Experimentelle Untersuchungen über die Beziehungen zwischen Blutdruck und Niere, *Arch f exper Path u Pharmacol* **177** 662-674, 1935 (b) Arnott, W M, Kellar, R J, and Matthew, G D Hypertension Associated with Experimental Serum Nephritis, *Edinburgh M J* **44** 205-217 (April) 1937 (c) Braun-Menendez, E Stase veineuse du rein normal ou enerve et hypertension arterielle, *Compt rend Soc de biol* **113** 461-462, 1933

21 Smith, H W, Rovenstine, E A, Goldring, W, Chasis, H, and Ranges, H A The Effects of Spinal Anesthesia on the Circulation in Normal, Unoperated Man with Reference to the Autonomy of the Arterioles, and Especially Those of the Renal Circulation, *J Clin Investigation* **18** 319-341 (May) 1939

22 Freyberg, R H, and Peet, M M The Effect on the Kidney of Bilateral Splanchnicectomy in Patients with Hypertension, *J Clin Investigation* **16** 49-65 (Jan) 1937

23 Snyder, J C The Cardiac Output and Oxygen Consumption of Nine Surgical Patients Before and After Operation, *J Clin Investigation* **17** 571-579 (Sept) 1938

The experiences outlined in this paper show that in the present series section of the splanchnic nerves fails in general to modify the prognosis. Those patients who had the most severe renal and retinal lesions (and the highest pressures) fared worst, those with minimal or no renal and retinal lesions fared best. In comparison with these criteria, the patient's age, the duration of the disease, presence of thickened larger arteries and lability of pressure (either spontaneous, in reaction to the cold test, or with the patient under the influence of sedative drugs) were of no significance whatsoever.

Of the present series of 40 patients, only 6 can be seriously considered as having had their prognoses altered by the operation. Of these, 2 (Mr McK and Mrs P) were remarkable chiefly for reduction in the systolic and the pulse pressure, the diastolic pressure being only temporarily lowered. Mr Y obtained a moderate reduction of pressure but averaged only 155 systolic and 110 diastolic before operation. While Mrs M's pressure has been as low as 110 to 120 systolic and 80 diastolic, such levels followed another operation and an attack of acute pulmonary edema. Mr L no longer has been observed to have "diencephalic" attacks, associated with such pressures as 245 systolic and 185 diastolic, but while the pressure level is lower, he remains incapacitated. Miss G, although her pressure did not fall appreciably until six months after operation, has had by far the best result, in spite of the fact that clinical signs of heart failure were present before, she now leads an almost unrestricted life. Three of these patients would not have been operated on had we adhered to the commonly accepted criteria for selection of patients.

Arterial hypertension is associated with two entirely different constellations of symptoms. Those of the first are in the nature of complications of the vascular lesions, i.e., headache from "brain edema," blurred vision in association with retinopathy, dyspnea accompanying left ventricular failure, substernal pain in persons with myocardial infarction, hemiplegia and the syndrome of uremia. The second set of symptoms consists of more vague complaints, such as weakness, palpitation, pounding in the arteries, dizziness and fatigability, and have been shown²⁴ to occur in nonhypertensive psychoneurotic patients with the same order of frequency as in patients with high arterial pressure.

Relief of any of this second group of symptoms without reduction of blood pressure is not a successful result, it has been shown repeatedly²⁵ that enthusiastic or dramatic therapeutic efforts are often rewarded

24 Ayman, D, and Pratt, J H. Nature of the Symptoms Associated with Essential Hypertension, *Arch Int Med* **47** 675-687 (May) 1931.

25 Ayman, D. An Evaluation of Therapeutic Results in Essential Hypertension. I. The Interpretation of Symptomatic Relief, *J A M A* **95** 246-249 (July 26) 1930.

by such relief. The only safe criterion of success is a complete cure, or at least a maintained significant²⁶ decrease of blood pressure. Even the latter may at times follow ordinary operations,²⁷ and in 1 of our patients as marked a reduction in pressure followed a hysterectomy as had occurred a year earlier after section of the splanchnic nerves.

SUMMARY AND CONCLUSIONS

Forty patients were observed who underwent section of the splanchnic nerves and removal of three pairs of lower thoracic ganglions, performed in order to relieve arterial hypertension. The criteria usually given for selection of patients were ignored.

From a consideration of what is known about the pathologic physiology of arterial hypertension and the effects of denervation it would seem that not much could be expected from any such denervating operations.

In general the results were poor. In only 1 patient was there a brilliant result, although in 5 others there was some degree of success in reducing blood pressure. Six more patients felt better but their arterial pressures were not lowered. In 9 patients there was no change. Eleven died within a year and a half, with their condition unchanged (transient relief of symptoms occurring in 5 of these). Eight died within two weeks of the operation.

Such criteria as age, duration of hypertension, vascular complications in the brain and the heart, heart failure and lability of arterial pressure were not prognostically significant. The main role in deciding the outcome seemed to be played by the presence or absence of malignant hypertension as evidenced by renal and retinal lesions.

26 Ayman, D. An Evaluation of Therapeutic Results in Essential Hypertension. II. The Interpretation of Blood Pressure Reductions, *J A M A* **96** 2091-2094 (June 20) 1931.

27 Volini, I. F., and Flaxman, N. The Effects of Nonspecific Operations on Essential Hypertension, *J A M A* **112** 2126-2128 (May 27) 1939.

STAPHYLOCOCCIC BACTEREMIA

TREATMENT WITH SULFAPYRIDINE AND SULFATHIAZOLE

WESLEY W SPINK, M D

Assistant Professor in Internal Medicine

ARILD E HANSEN, M D, P H D

Associate Professor in Pediatrics

AND

JOHN R PAINE, M D, P H D

Assistant Professor in Surgery

MINNEAPOLIS

Invasion of the blood stream by staphylococci often is attended with serious consequences. In a recent review, Mendell¹ collected from the literature 279 cases of staphylococcic septicemia and added 35 of his own. He found the mortality rate in these 314 cases to be 77 per cent. This high death rate approximates the experience of most physicians, and because of it there have been many attempts to combat this type of infection with various specific therapeutic agents.

It is now generally recognized that the high mortality rate is due in part to potent exotoxins elaborated by certain strains of staphylococci, which are disseminated through the blood and tissues. According to several reports,² it would appear that the prompt administration of specific staphylococcus antitoxin is an effective method for treating this toxemia. However, this form of serotherapy has certain limitations.

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From the Departments of Internal Medicine, Pediatrics and Surgery of the University of Minnesota Hospitals and Medical School.

1 Mendell, T H. Staphylococcic Septicemia, *Arch Int Med* **63** 1068 (June) 1939.

2 Parish, H J, and Clark, H M. Staphylococcal Toxin and Antitoxin, *J Path & Bact* **35** 251, 1932. Dolman, C E. Staphylococcus Antitoxic Serum in the Treatment of Acute Staphylococcal Infections and Toxaemias, *Canad M A J* **31** 1 and 130, 1934. Joyner, A L, and Smith, D T. Acute Staphylococcus Osteomyelitis. The Use of Staphylococcus Antitoxin as Aid to Management of Toxemia and Staphylococemia, *Surg, Gynec & Obst* **63** 1, 1936. Robertson, D E. Acute Hematogenous Osteomyelitis, *J Bone & Joint Surg* **20** 35, 1938. Baker, L D, and Shands, A R, Jr. Acute Osteomyelitis with Staphylococemia, *J A M A* **113** 2119 (Dec 9) 1939. Stookey, P F, and Scarpellino, L A. Staphylococcus Septicemia, *South M J* **32** 173, 1939.

Some highly invasive strains of staphylococci produce little or no exotoxin³. Furthermore, while the antitoxin neutralizes the exotoxin, it does not directly affect the bacteria. The potency of staphylococcus antitoxin is usually based on its antihemolytic titer. Valentine and Butler⁴ expressed the belief that a more effective antitoxin would be one with its potency based on its antileukocidin content. Recently, still another form of serotherapy has been advocated. Julianelle and Wieghard⁵ found that all pathogenic strains of staphylococci possessed, in common, an intracellular polysaccharide. Subsequently, Julianelle observed that the serums of patients with severe staphylococcic infections contained precipitins for this polysaccharide. Encouraging results have followed the treatment of patients having staphylococcic septicemia with an immune rabbit serum containing a high titer of precipitins for this carbohydrate fraction of staphylococci⁶.

There has been continued interest in the use of bacteriophage for staphylococcemia, but this form of therapy has but few enthusiastic followers. On the other hand, due consideration must be given to the recent report of Longacre, Zaytzeff-Jern and Meleney,⁷ who, in a group of 21 patients with staphylococcic septicemia treated with bacteriophage, found the mortality rate to be 28.5 per cent. This compared favorably with their control group of 54 patients, which had a mortality rate of 81.4 per cent. Albee⁸ recommended the local and parenteral use of bacteriophage in the treatment of osteomyelitis and septicemia.

Various forms of chemotherapy have been championed for years, with only equivocal results. Arsenicals, especially neoarsphenamine, have been widely used in the treatment of staphylococcic sepsis involving the urinary tract. Osgood⁹ pointed out that the antistaphylococcic action of neoarsphenamine is greater than that of equivalent amounts of sulfanilamide or sulfapyridine when added to bone marrow cultures contain-

3 Blair, J. E. The Pathogenic Staphylococci, *Bact. Rev.* **3** 97, 1939.

4 Valentine, F. C. O., and Butler, E. C. B. Specific Immunity in Acute Staphylococcal Osteomyelitis, *Lancet* **1** 973, 1939.

5 Julianelle, L. A., and Wieghard, C. The Immunological Specificity of Staphylococci. I. The Occurrence of Serological Types, *J. Exper. Med.* **62** 11, 1935.

6 Julianelle, L. A. Observations on the Specific Treatment (Type A Antiserum) of Staphylococcal Septicemia, *Ann. Int. Med.* **13** 308, 1939.

7 Longacre, A. B., Zaytzeff-Jern, H., and Meleney, F. L. The Treatment of Staphylococcus Septicemia with Bacteriophage, *Surg., Gynec. & Obst.* **70** 1, 1940.

8 Albee, F. H. The Treatment of Osteomyelitis and Septicemia by Bacteriophage, *Rocky Mountain M. J.* **35** 43, 1938.

9 Osgood, E. E. Effectiveness of Neoarsphenamine, Sulfanilamide, Sulfapyridine in Marrow Cultures with Staphylococci and Alpha Streptococci, *Proc. Soc. Exper. Biol. & Med.* **42** 795, 1939.

ing staphylococci. In view of this observation, the therapeutic value of neoarsphenamine in treatment of patients with septicemia merits further investigation.

The value of chemotherapy for staphylococcic sepsis has been greatly enhanced by the results of investigations with sulfanilamide and its various derivatives. While it has been shown that under certain in vitro conditions sulfanilamide is bacteriostatic and bactericidal for staphylococci,¹⁰ the drug is of doubtful value in the treatment of septicemia, even though Thornhill and his associates¹¹ recorded the recovery of 2 patients following the use of sulfanilamide. It has been stated that in vitro sulfanilamide inactivates the exotoxin of *Staphylococcus aureus*.¹² More recently, Bayliss¹³ reported that sulfanilamide, sulfapyridine and sulfathiazole (2-sulfanilamidothiazole) failed to inactivate in vitro the toxic manifestations of staphylococci. There is accumulating experimental and clinical evidence that sulfapyridine is definitely superior to sulfanilamide in the treatment of staphylococcic septicemia. Sulfapyridine offers greater protection than sulfanilamide to mice infected with fatal doses of *Staph. aureus*.¹⁴ Numerous case reports are available describing the successful use of sulfapyridine in the treatment of patients with septicemia.¹⁵ Blake and Haviland¹⁶ found this agent to be of doubtful value in the treatment of 5 patients. It would seem that still more promising results may be anticipated with the use

10 Spink, W. W. The Bactericidal Effect of Sulfanilamide upon Pathogenic and Non-Pathogenic Staphylococci, *J. Immunol.* **37** 345, 1939.

11 Thornhill, W. A., Jr., Swart, H. A., and Reel, C. Sulfanilamide in Staphylococcic Septicemia. Two Cases with Recovery, *J. A. M. A.* **113** 1638 (Oct. 28) 1939.

12 Carpenter, C. M., and Barbour, G. M. Inactivation of Toxins to *Staphylococcus aureus* and *Clostridium Welchii* in Vitro by Sulfanilamide, *Proc. Soc. Exper. Biol. & Med.* **41** 354, 1939.

13 Bayliss, M. Effect of Sulfanilamide, Sulfapyridine and Sulfathiazole on Staphylococcus Toxins, *Proc. Soc. Exper. Biol. & Med.* **44** 525, 1940.

14 Whitby, L. E. H. Chemotherapy of Bacterial Infections, *Lancet* **2** 1095, 1938. Bliss, E. A., and Long, P. H. Comparative Therapeutic Effects of Sulfapyridine in Experimental Staphylococcus Aureus Infections in Mice, *Proc. Soc. Exper. Biol. & Med.* **40** 32, 1939.

15 Fenton, W. J., and Hodgkiss, F. Staphylococcal Septicemia Treated by M & B 693, *Lancet* **2** 667, 1938. O'Brien, E. J., and McCarthy, C. J. Staphylococcal Septicemia Treated with M & B 693, *ibid.* **2** 1232, 1938. Maxwell, J. Staphylococcal Septicemia Treated with M & B 693, *ibid.* **2** 1233, 1938. Wade, H. J. Staphylococcic Septicemia Treated with Sulfapyridine, *ibid.* **1** 756, 1939. McConney, F. S. A Case of Staphylococcus Haemolyticus Septicemia Treated with Dagenan, *Canad. M. A. J.* **41** 67, 1939. Goldberg, S. L., and Sachs, A. Sulfapyridine in the Treatment of Staphylococcus Aureus Bacteremia, *J. A. M. A.* **113** 1639 (Oct. 28) 1939.

16 Blake, F. G., and Haviland, J. W. Sulfapyridine in Pneumococcal, Streptococcal and Staphylococcal Infections, *Tr. A. Am. Physicians* **54**.130 1939.

of sulfathiazole in the treatment of septicemia. The *in vitro* bacteriostatic action of sulfathiazole on staphylococci is more pronounced than that observed for sulfapyridine.¹⁷ Sulfathiazole has been shown to be more efficient than sulfapyridine in protecting mice against lethal doses of *Staph aureus*.¹⁸ Few clinical reports are available concerning the therapeutic value of sulfathiazole in the treatment of staphylococcic septicemia in human beings. Fitch¹⁹ successfully treated with sulfathiazole a child who had staphylococcic septicemia and pyemia. Stirling²⁰ used sulfathiazole effectively in the treatment of an elderly person with staphylococcic septicemia. In a preliminary report for the Council on Pharmacy and Chemistry of the American Medical Association, Long²¹ stated that sulfathiazole was as effective as sulfapyridine, if not more so, in the treatment of human staphylococcic infections.

During the past three years, we have observed 100 patients with various types of staphylococcic sepsis. Staphylococci were isolated from the blood streams of 50 of these patients. Twenty-five of these patients having staphylococcemia are included in this report. Either sulfapyridine or sulfathiazole or both were administered to the latter group.²²

Ten patients were treated with sulfapyridine. Pertinent clinical data and the results of therapy are shown in table 1. Four of the patients in this group died, a mortality of 40 per cent. There was some variation in the dose of the drug that was used, but the usual procedure was to administer orally 4 Gm. as an initial dose and then 1 Gm. every four hours.²³ Equivalent doses of sodium bicarbonate were given at the same time. Sodium sulfapyridine was given intravenously to only 1 patient,

17 Lawrence, C. A. Bacteriostatic Actions of Three Thiazol Derivatives of Sulfanilamide upon Bacteria in Broth Cultures, *Proc Soc Exper Biol & Med* **43** 92, 1940. Long, P. H., and Bliss, E. A. Bacteriostatic Effects of Sulfathiazole upon Various Micro-Organisms. Its Therapeutic Effects in Experimental Pneumococcal Infections, *ibid* **43** 324, 1940. Rammelkamp, C. H., and Keefer, C. S. Sulfathiazole. Effect on *Staphylococcus Aureus* in Vitro, *ibid* **43** 664, 1940.

18 Rake, G., and McKee, C. M. Action of Sulfathiazole and Sulfamethylthiazole on *Staphylococcus Aureus*, *Proc Soc Exper Biol & Med* **43** 561, 1940. Bliss, E. A., and Ott, E. Effect of Sulfapyridine, Sulfathiazole and Sulfamethylthiazole upon Severe Staphylococcal Infection in Mice, *ibid* **43** 706, 1940.

19 Fitch, T. S. P. Sulfathiazole in *Staphylococcus Aureus*. Epidural Abscess with Septicemia and Pyemia, *Arch Pediat* **57** 119, 1940.

20 Stirling, W. C. Sulfathiazole. Two Cases of Septicemia with Recovery, *J A M A* **115** 118 (July 13) 1940.

21 Long, P. H. Sulfathiazole and Sulfamethylthiazole, *J A M A* **114** 870 (March 9) 1940.

22 Sulfapyridine was supplied by Merck & Co., Inc., sodium sulfapyridine, by the Calco Chemical Co., sulfathiazole and sodium sulfathiazole, by the Squibb Institute for Medical Research.

23 In children the average daily dose was 0.25 Gm. per kilogram of body weight.

TABLE 1.—Patients with Staphylococci Bacteremia Treated with Sulfapyridine

Patient		Diagnoses in Addition to Bacteremia	Primary Focus	Source of Staph. Aureus Cultures	Total Dose, Gm	Blood Concentration, Mg per 100 Cc	Free	Total	Toxic Reactions	Additional Therapy	Comment
No	Age Sex				Days						
1	15 ♂	Subcutaneous abscesses	?	Blood, abscesses	1450	15	84	95	Nausea and vomiting	Multiple transfusions, pentaceneolide administered intramuscularly	Recovery, marked leukopenia on entry, leukocytes 800 coccid in cytoplasm of leukocytes, reentry 6 mo later with lymphatic leukemia
2	15 ♂	Diabetes mellitus, carbuncle, metastatic abscesses	Carbuncle	Blood, urine, abscesses	1070	63	112	220	Anemia, mental confusion	Sulfanilamide for 14 days without effect, fusions, on second admission neorsphenamine	Recovery, diabetic coma, reduced renal function due to abscesses, successful use of neorsphenamine
3	11 ♂	Subphrenic abscess	?	Blood, subphrenic space	340	8	10	80	Nausea and vomiting	Sulfanilamide for 18 days, spleen cast, left hip Body cast	Recovery
4	11 ♀	Chronic osteomyelitis	Lesion of femur	Draining sinus, left femur	570	10	28	53	None		Recovery
5	17 ♀	Acute osteomyelitis, lung abscesses, meningitis, arthritis	?	Urine, blood, draining sinus, leg	370	10	101	134	Vomiting		Recovery
6	12 ♂	Acute bacterial endocarditis	?	Blood	74	12 hr	80	92	None		Recovery
7	25 ♀	Acute osteomyelitis	Laceration of foot	Blood, lesion on foot	260	8	32	89	None		Death, no improvement following use of drug
8	68 ♂	Subacute bacterial endocarditis, mitral stenosis	?	Blood	1503	64	38	40	None		Death, drop in temperature after administration of sulfapyridine (7.2 Gm) intravenously
9	68 ♂	Extensive necrosis of right foot, metastatic abscesses	Nail puncture, right foot	Blood, lesion on foot	13	55	62	64	None	Tetanus antitoxin 11,500 units (prophylactic), multiple transfusions, neorsphenamine	Recovery, desperate illness, coma, meningismus
10	57 ♂	Chronic osteomyelitis, lung abscesses, suppurative myocarditis, perinephritic abscess	Puncture wound of finger from fish bone	Blood, lesion on finger	625	17	37	41	54	Sulfanilamide for 15 days	Definite improvement, blood culture sterile, 17 mo after onset of illness, death
11	11				110	11	22	29	None	Amputation of foot because of necrosis, tetanus and gas bacillus antitoxin (prophylactic)	Recovery
12	11									Multiple transfusions, sulfanilamide, without effect	Death, patient moribund on admission

in the form of a 5 per cent solution in distilled water. As the temperature became normal and the blood cultures remained sterile, the dose was reduced over a period of several days. Some comment is necessary concerning the 4 patients who died. Patient 5 had many metastatic lesions and severe pyemia. Although she received 37 Gm of sulfapyridine in ten days and the level of free sulfapyridine in the blood was 10.1 mg per hundred cubic centimeters, she became progressively worse and finally died. Patient 10 likewise had severe pyemia and was moribund on entry to the hospital. Patient 6 was in a comatose condition when first treated. She received a total of 72 Gm of sodium sulfapyridine in twelve hours. Although her temperature declined after this therapy, no further improvement was observed. Postmortem examination revealed bacterial vegetations on the mitral valve and myocardial abscesses. Patient 8 was under observation for eleven months. When first seen, she presented the signs and symptoms of subacute bacterial endocarditis. After the administration of sulfapyridine, she became afebrile and the blood cultures remained sterile. She returned home and was apparently in good health for five months. However, shortly before her second admission, she suffered from a cerebral embolus and staphylococci were isolated from her blood stream. She failed to improve and died seventeen months after the onset of the illness. Staphylococci were obtained from the mitral vegetations at autopsy. In the remaining 6 patients, who recovered, the blood streams were sterilized after the administration of sulfapyridine. On entry, patient 1 was acutely ill with an infection of the blood stream, however, we were unable to determine the primary focus of the infection. The leukocytes in his blood totaled 800 per cubic millimeter. Examination of Wright-stained blood smears revealed cocci in the cytoplasm of the polymorphonuclear neutrophilic leukocytes. It was of interest that after sulfapyridine had been given for several days staphylococci disappeared from the blood stream and that at the same time there was a marked increase in the circulating leukocytes. He reentered the hospital six months after recovery from this infection, at which time he had lymphatic leukemia. The leukemia was not in evidence during the previous period of hospitalization. His blood cultures remained sterile during the second period of observation. Patient 2 entered the hospital in a state of severe diabetic acidosis. He had a large carbuncle on his neck, and staphylococci were isolated repeatedly from his blood. After sulfapyridine therapy the staphylococcemia disappeared and he recovered. He reentered the hospital two months later complaining of chills and fever, pyuria and dysuria, cultures of the blood and urine showed the presence of staphylococci. Because of the reduced renal function, presumably due to multiple nephritic abscesses, neosalphenamine was given intravenously

instead of sulfapyridine. He recovered completely and has been in excellent health for the past seven months. Sulfanilamide was given to patients 2, 4, 8 and 10, without any demonstrable benefit.

Fifteen consecutive patients were treated with sulfathiazole (table 2). Essentially the same oral doses were employed as for sulfapyridine. It is to be noted that lower concentrations in the blood were attained with sulfathiazole than with sulfapyridine. The blood was sterilized in all 15 patients after the use of sulfathiazole, and all recovered from their acute infections. Patient 23 died subsequently of complicating myelogenous leukemia. Patients 12, 13, 23 and 24 also received sulfapyridine prior to the use of sulfathiazole. In patient 12, the temperature decreased after the administration of sulfapyridine, but the bacteremia persisted. Sulfapyridine had no beneficial effect in patient 13, while it appeared to be equally as effective as sulfathiazole in patient 23. When sulfapyridine was administered to patient 24, clinical improvement followed, but the temperature remained elevated. Sulfanilamide had been administered before sulfathiazole to patients 13, 17, 19, 20 and 23, without any improvement.

COMMENT

It is apparent from the foregoing data that sulfathiazole is superior to either sulfanilamide or sulfapyridine in the treatment of patients with staphylococcemia. It should be emphasized that although sulfathiazole will sterilize the blood stream, viable organisms will persist in localized abscesses and metastatic lesions. Therefore, as an adjunct to therapy with sulfathiazole it is imperative that abscessed areas be adequately drained. While the drug will not sterilize the contents of an abscess, there is clinical evidence that it will aid in preventing the spread of the infection to healthy tissue and the consequent dissemination of bacteria to the blood stream. Any patient who has been successfully treated for septicemia, but in whom foci of infection persist, must be kept under observation for a long period, because invasion of the blood stream may recur.

It is difficult to state what concentration of either sulfapyridine or sulfathiazole in the blood will give the maximum therapeutic effect. In the sulfapyridine-treated patients the levels of the free drug averaged about 6 mg per hundred cubic centimeters, while in the group receiving sulfathiazole the concentrations were definitely less than this. Further investigation is necessary before definite recommendations can be made.

Sulfathiazole appears to be a drug that can be given with a reasonable degree of safety. In the present series of patients, its administration resulted in nausea and vomiting in but 3 and in nausea alone in a fourth. In 3 of the patients who received sulfathiazole dermatitis developed. In 2 of the patients the eruption was maculopapular while

TABLE 2—*Patients with Staphylococcic Bacteremia Treated with Sulfathiazole*

Patient No	Age	Sex	Diagnoses in Addition to Bacteremia	Primary Focus	Source of Staph. Aureus Cultures	Total Dose, Gm	Sulfathiazole				Toxic Reactions	Additional Therapy	Comment
							Days	Free	Total	Blood Concentra- tion, Mg per 100 Cc			
11	31	♀	Suppurative mastitis	Infection of the upper respira- tory tract, sinusitis	Blood, right breast	25	5	18 43	26 50		Nausea and vomiting	Simple mastectomy	Recovery
12	40	♂	None	?	Blood	40	14	53 56	63 68		None	Sulfapyridine for 7 days, drop in tempera- ture, persistence of bacteremia	Recovery, no primary or metastatic lesions demonstrated
13	20	♂	Carbuncle, cellulitis	Carbuncle	Blood	25	8				None	Sulfanilamide and intra- venous administration of sulfapyridine, with out effect	Recovery, temperature 106 F when sulfathiazole first administered
14	20	♂	Suppurative arthritis, right hip	?	Blood, hip joint	144	25	30 30 38 33 43	34 36 44 42 52		None	Aspiration of right hip joint, spleen cast, right hip	Recovery, temperature 103.5 F to normal in 72 hr, still contained Staph. aureus in material draining from right hip
15	15	♂	Early osteomyelitis, left tibia	?	Blood	129	21	20 38 25 12	25 46 29 16		None	Cast and elevation of extremity	Recovery, temperature 105.4 F to normal in 48 hr, drug continued to prevent possi- ble spread of osteomyelitis
16	38	♂	Chronic empyema, diabetes mellitus, pyelonephritis	?	Blood, urine	37	8	25 38	34 48		None	Rib resection for empyema, insulin	Recovery, temperature 105 F to normal in 12 hr, cul- tures of urine sterile development of broncho- pleural fistula

17	21	♀	Septic abortion with metastatic abscesses	Uterus	Blood	119	20	None	Sulfanilamide for 5 days, development of jaundice, drainage of subcutaneous abscesses	Recovery, temperature 105 F to normal gradually in 18 days
18	9	♂	Suppurative arthritis, left knee, fractured left patella	Furuncle	Blood, knee joint	123	28	18	40	Recovery, drug continued 2 weeks after appearance of dermatitis, no further toxic signs
19	19	♂	Peritonitis, perforated appendix	Appendiceal abscess	Blood	99	14	11	38	Recovery, interval appendectomy scheduled
20	2 wk	♂	Omphalitis, pyoderma, otitis media	Umbilicus	Blood, ear, nose, umbilicus	125	15	41	32	Recovery
21	51	♂	Muscle abscesses	Infection of the upper respiratory tract	Blood, hip joint	56	8	22	15	Recovery, abscesses not drained
22	15	♂	Osteoarthritis, right hip	Infection of the upper respiratory tract	Blood, hip joint	47	13	52	52	Recovery, Staph aureus still contained in material draining from right hip
23	33	♂	Pyoderma, myelogenous leukemia	Carbuncle	Blood, skin lesion	40	20	34	27	Recovery, death from leukemia 6 mo later, blood sterile after sulfapyridine and sulfathiazole
24	29	♀	Septic abortion, peritonitis	Uterus	Blood	30	5	None	Sulfapyridine effective, but fever persistent	Recovery, temperature 103 F to normal in 5 days after sulfathiazole
25	77	♀	Chronic osteomyelitis with multiple lesions	?	Blood	60	20	52	33	Recovery
								39	21	
								39	19	

in the third (patient 18) it had the appearance of an erythema nodosum-like lesion. It is of interest that we discontinued the administration of the drug in the latter patient until the cutaneous lesions had disappeared and that then the same doses were resumed for several days without a recurrence of the dermatitis. In a larger series of patients treated with sulfathiazole, dermatitis was found to be the most frequent toxic reaction to this drug.²⁴

SUMMARY

Ten patients with staphylococcic bacteremia were treated with sulfapyridine. Six of the patients recovered.

Fifteen patients were treated with sulfathiazole, in all of whom the blood was successfully sterilized. Only 1 patient died subsequently, his death was due to myelogenous leukemia.

Sulfathiazole appears to be the best therapeutic agent that we have at present for this type of infection and can be administered with a reasonable degree of safety.

NOTE—Since this report was submitted for publication, 4 additional children having staphylococcic bacteremia have been treated with sulfathiazole. Three of them recovered, while the fourth died.

Patient 26, a 9 year old girl, had osteomyelitis involving the right foot. *Staph aureus* was isolated from the blood stream on four occasions. After the administration of sulfathiazole there was marked improvement in her clinical condition, which permitted surgical drainage of the involved bone. At the time she left the hospital there was still some purulent discharge from the local lesion. Patient 27, a 12 year old girl, had acute osteomyelitis of the lower part of the right tibia. When she entered the hospital it was believed that she had tetanus, because of convulsions and other clinical features. Four successive blood cultures contained *Staph aureus*. After medication with sulfathiazole there was dramatic improvement in her condition, and blood cultures remained sterile. A drug dermatitis ensued, and sulfapyridine was prescribed. Several weeks after recovery osteomyelitis appeared in the left tibia, indicating a second invasion of the blood stream while she was receiving sulfapyridine. Patient 28, an 11 year old girl, suffered from severe cellulitis of the right side of the face, originating from a small furuncle in this area. Blood cultures yielded *Staph aureus* four times. On one occasion there were 12 colonies per cubic centimeter of blood. Although adequate doses of sulfathiazole were administered, she remained acutely ill. On the fifth day of her stay in the hospital, she received 100,000 units of staphylococcus antitoxin intravenously. During the next three days an additional 180,000 units was given. Coincident with the combined use of sulfathiazole and antitoxin, the blood stream became sterile, and there was marked improvement in her condition. She left the hospital twenty-eight days after admission. In patient 29, a 14 year old boy, thrombophlebitis of the right leg developed five days before admission to the hospital. Prior to this he had had recurrent furunculosis. *Staph aureus*

²⁴ Spink, W. W., and Hansen, A. E. Sulfathiazole. Clinical Evaluation, J. A. M. A. **115** 840 (Sept 7) 1940.

was isolated from his blood cultures five times. The same organism was obtained from the cerebrospinal fluid. Sulfapyridine was administered in large doses, and the level of free sulfapyridine in the blood rose to 213 mg per hundred cubic centimeters. Antitoxin was given intravenously. He also received sulfathiazole. However, his condition became progressively worse, and he died on the ninth day of his stay in the hospital. Postmortem examination revealed an extensive pyemic process with multiple abscesses present throughout the entire body. It is of interest that in vitro studies carried out with the strain of staphylococcus isolated from the patient's blood showed that it was much more susceptible to the bacteriostatic action of sulfathiazole than that of sulfapyridine.

ENTERORRHAGIA COMPLICATING LOBAR PNEUMONIA

ACUTE PNEUMOCOCCIC HEMORRHAGIC ULCERATIVE GASTRO-ENTERITIS, WITH REPORT OF A CASE

JOSEPH P McCracken, M D
BOSTON

The occurrence of gastrointestinal hemorrhage in the course of pneumonia is not mentioned in the most recent American textbooks of medicine or treatises on pneumonia. However, according to the foreign literature (and it is here that the great majority of cases of such a condition are described) this condition is a fairly well known complication of pneumonia.

Aversa¹ attributed the first observations of enterorrhagia in the course of pneumonia to Ponfick, Jaksch, Engel and Dittrich, later there was confirmation by Brinton and Berthold. Aversa reported these instances of the condition as having occurred prior to 1887 but did not list references.

Dieulafoy,² in 1887, recorded 2 cases with pathologic reports. The first was one of lobar pneumonia during the course of which there occurred abdominal pain and hematemesis, followed by melena. Necropsy showed multiple acute ulcerations, from the size of a pinpoint to 3 mm in diameter, located chiefly in the pyloric region of the stomach. Pneumococci were found in the edge of the ulcers and in the nearby interglandular connective tissue. The second case was that of a patient who complained of severe abdominal pain on the eighth day after the onset of lobar pneumonia, vomited 1 liter of blood and died on the nineteenth day, of pneumococcic endocarditis and meningitis. At autopsy no gross ulcerations of the stomach were noted, but microscopic section showed small hemorrhagic foci in the submucosa and, more abundantly, in the interglandular tissue. Search for micro-organisms was reported as fruitless, and there were no signs of an inflammatory reaction. To this

From the Department of Medicine, Emory University School of Medicine, Atlanta, Ga.

1 Aversa, T. Emorragie del tubo digerente durante il decorso delle pneumoniti, *Pediatria* 46 628 (July) 1938.

2 Dieulafoy, G. Clinique médicale de l'Hotel-Dieu de Paris, Paris, Masson & Cie, 1887, lesson 17, cited by Aversa¹.

intercurrence of gastric hemorrhage in lobar pneumonia Dieulafoy gave the name "pneumococcic hemorrhagic ulcerative gastritis"

Griffon,³ in 1899, cited another case in which at autopsy both gastric and intestinal hemorrhagic ulcerations were observed but no bacteria were found in the ulcers Rathery⁴ cited a similar case of enterorrhagia in 1901, but the outcome was not described

In 1913 de Sandro⁵ described a case of lobar pneumonia in which, after eight days of illness, a severe intestinal hemorrhage intervened, preceded and accompanied by abdominal pain, muscular rigidity and tenesmus and followed by severe circulatory collapse and exsanguination He applied the name "pneumococcic hemorrhagic ulcerative enteritis" to this complication

Chatard⁶ in 1926 found only 8 cases recorded in the French literature He discussed a study made by Schneider in 1905, in which the following classification of intestinal complications of pneumonia was made (1) simple enteric, (2) dysenteric and (3) ulcerative hemorrhagic The simple enteric type is characterized by tympanites with accompanying respiratory embarrassment and is considered to be due to profound toxemia The dysenteric type, in which the name is self explanatory, shows the tenesmus, the blood-streaked stools and the other manifestations of acute dysentery Chatard, however, subdivided the third type into the ulcerative and the hemorrhagic The ulcerative type usually does not give rise to immediate clinical symptoms unless it be perforation of the intestines, of which only 1 case was mentioned The hemorrhagic type may simply occur in combination with the ulcerative type or may be completely autonomous The blood passed is fresh or is transformed during its passage through the intestine before making itself evident as a tarry stool

Chatard⁶ cited the case of a man who had a large intestinal hemorrhage in an acute illness but in whom the focus of infection could not be found However, three weeks later pneumococcic empyema was identified A blood culture was sterile, but the pneumococci were recovered in a culture of the urine

3 Griffon *Ulcérations hémorragiques de l'estomac et double ulcération térébrante du duodénum au cours d'une pneumonie suppurée*, Bull et mém Soc anat de Paris **1** 611, 1899, cited by Aversa¹

4 Rathery *Hémorragie intestinale dans un cas de pneumonie*, Bull et mém Soc méd d hôp de Paris **18** 976, 1901, cited by Aversa¹

5 de Sandro, D *Contributo allo studio delle enterorragie pneumoniche* Polichinico (sez med) **20** 306, 1913, cited by Aversa¹

6 Chatard, J *Case of Intestinal Hemorrhage in Pneumococcal Infection with Clinical Remarks*, M J & Rec **123** 453 (April 7) 1926

The first case of intestinal hemorrhage complicating pneumonia described in the American literature is that reported by Johnson⁷ in 1929. This was the case of a 12 year old boy who suddenly had a large (500 cc) intestinal hemorrhage on the fourth day of "influenzal pneumonia." In Johnson's experience it had not been unusual for patients with influenza to have slight bleeding from the intestine, but in no other case had he seen such copious hemorrhage, which he concluded was an unusually severe manifestation of influenzal congestion of the intestine.

In July 1930 Lesne, Heimann and Lièvre⁸ reported 2 cases of enterorrhagia occurring in children in the course of pneumococcic pneumonia. In the first case the child recovered after transfusion, but in the second, that of a 28 month old baby, the child died and at autopsy it was not possible to define any lesion that could justify the intervening hemorrhage. Blood cultures were sterile. In the same report 2 additional cases of the condition in children were described by Guillemot, Prieu and Barbé.

Lorando,⁹ in 1934, reported a case of a 78 year old man with diabetes in which pneumonia occurred and was followed by melena with a fatal hemorrhage five days later. Necropsy showed a small ulceration in the pylorus of the stomach. Lorando attributed the hemorrhage to the action of the toxin of the virus on the capillaries.

More recently Lambrinacos¹⁰ and Aversa¹ have recorded cases of intestinal hemorrhage occurring in the course of lobar pneumonia.

In none of the aforementioned cases was the type of the pneumococcus determined. In 1938, in a report of 2 cases by Sanford, Hughes and Weems,¹¹ the pneumococcus was recorded as type IV in each case. In the first case, the pneumococci were recovered from the blood stream and autopsy revealed a large (4 cm) ulcer in the fundus of the stomach with six smaller ones nearby. In the other case, the blood cultures were sterile and the patient recovered after a moderate enterorrhagia.

7 Johnson, W M. Intestinal Hemorrhage as a Complication of Pneumonia, *Arch Pediat* **46** 193 (March) 1929.

8 Lesne, E., Heimann, and Lièvre, J A. Hemorragie intestinale et pneumonie, *Bull Soc de pédiat de Paris* **28** 420 (July) 1930, cited by Aversa¹.

9 Lorando, N. Sur un cas d'hémorragie gastro-intestinale chez un diabetique atteint de pneumonie grippale, *Bull et mem Soc méd d hop de Paris* **50** 1080, 1934, cited by Aversa¹.

10 Lambrinacos. Un cas d'enterorragie chez un enfant atteint de pneumonie, *Bull Soc de pediat de Paris* **35** 257 (April) 1937.

11 Sanford, C H., Hughes, J D., and Weems, J. Pneumonia Complicated by Acute Pneumococcic Hemorrhagic Ulcerative Gastroenteritis (Dieulafoy's Erosion), *Arch Int Med* **62** 597 (Oct) 1938.

REPORT OF CASE

J G, a 19 year old Negro, was admitted to the Negro unit of Grady Hospital on Sept 28, 1938, complaining of a head cold and a sore throat, of one week's duration. There was an associated cough productive of purulent sputum. His past health had always been excellent, with no history of nausea, indigestion, abdominal pain, hematemesis, icterus or bloody or tarry stools.

On admission, he was well developed and well nourished but dehydrated and in acute distress. The rectal temperature was 104 F, the pulse rate 110 and the respiratory rate 24. The blood pressure was 124 systolic and 84 diastolic. The skin was dry and hot and the facies anxious. The nasal turbinates were edematous and injected. Herpes simplex was present about the mouth. The pharynx was acutely inflamed. The cervical lymph nodes were bilaterally enlarged and tender. The heart was normal, and the lungs were entirely clear. Moderate abdominal distention with active peristalsis was noted.

The day after admission the patient had a shaking chill, and on September 30 pain, aggravated by respiration, developed in the right lower part of the chest. Examination at this time revealed signs of early pneumonia in the lower lobe of the right lung, which progressed until October 2, when frank consolidation, confirmed by roentgen examination, became evident. At this time there was noted tenderness in the epigastrium and right upper quadrant of the abdomen. The complaint of epigastric pain continued until October 4, at which time the patient became semicomatose. On the afternoon of October 5, the sixth day of his pneumonia, he passed about 500 cc of semiliquid, tarry stool. At that time the blood pressure was 116 systolic and 68 diastolic. The abdomen was soft, with involuntary resistance and tenderness in the right upper quadrant. The apparently moribund condition persisted from the sixth to the eighth day of illness. On October 7, the eighth day of his pneumonia, he was much improved, the temperature having declined by lysis. The stools had returned to normal and showed no occult blood. Laboratory data showed the initial leukocyte count of 24,000 had risen to 35,000 at the height of the pneumonia and subsided to normal after the acute illness. Attempts to type the pneumococci in the sputum were unsuccessful. Blood cultures made at the onset of pneumonia were sterile. The rectal temperature during the first five days of his stay in the hospital ranged between 103 and 105 F, but dropped suddenly to 101 F two days prior to enterorrhagia and then returned by lysis to normal four days after the first decrease. When diet was resumed it was restricted to milk and alkaline powders and was progressively increased first to a soft and then to a regular diet a few days later. Roentgenographic studies failed to show any evidence of ulceration in the gastrointestinal tract. Since discharge the patient has been followed in the medical outpatient clinic and has shown no further complication.

Summary—The case is reported of a 19 year old boy in whom, after acute nasopharyngitis, lobar pneumonia developed. On the sixth day of the pneumonia, after complaining of pain in the upper part of the abdomen, he passed a large tarry stool. No further gastrointestinal bleeding occurred, and he recovered. Roentgenographic investigation of the stomach and intestines after the administration of barium revealed no ulceration. In view of no previous history of peptic ulcer, no evidence of hepatic disease and no presence of a blood dyscrasia, it is reasonable to include this case under the disease entity acute pneumococcal hemorrhagic ulcerative gastroenteritis.

COMMENT

An attempt has been made to summarize the data from the aforementioned cases. A complete analysis of all cases could not be made since some were only cited and others were incompletely described. However, enough data have been assembled to be of value in the study of the condition now known as acute pneumococcic hemorrhagic ulcerative gastroenteritis.

Age—The youngest patient whose case was reported was a 28 month old baby, whereas the oldest was a 78 year old man with diabetes. The age of the patient was between 6 and 26 in 60 per cent of the 10 cases in which it was stated.

Sex—The incidence of enterorrhagia was much greater among male than among female patients, for it occurred in male patients in 9 of the 12 cases in which sex was mentioned.

Occurrence of the Bleeding—In 12 cases the time of manifestation of the gastrointestinal bleeding was cited. This ranged from three to twenty-seven days after the onset of the pneumonia. In the case reported by Chatard the enterorrhagia occurred three weeks and was repeated two weeks prior to the recognition of existing pneumococcic empyema. Six to eight days after the onset of the pneumonia was the average time recorded for the occurrence of the enterorrhagia.

Signs and Symptoms—(a) *Abdominal Pain*. This was emphasized in 6 cases, the pain being either in the epigastrium or in the right upper quadrant of the abdomen or in both regions. There was also muscular rigidity in the case of de Sandro and in the one reported in this paper. The other writers did not make a statement as to the presence or absence of abdominal discomfort.

(b) *Melena*. This was present in all cases cited. In 3 hematemesis was also noted. In those cases which were fully described, signs of shock usually were associated with or appeared after the gastrointestinal bleeding. In a few cases (Chatard,⁶ Rathery,⁴ Aveisa,¹ and the case reported here) there was a drop in temperature previous to the recognition of the bleeding, but this was not true in the other cases.

Mortality—Of the 24 cases thus far reported, the outcome is definitely known in 13. In 6 it was fatal and in 7 recovery was made.

Pathologic Observations—Autopsies were reported in 6 cases. In the first case reported by Dieulafoy¹² there were multiple acute ulcera-

12 Dieulafoy, G. (a) *A Text-Book of Medicine*, ed 15, New York, D Appleton and Company, 1911, p 658, (b) *Gastrite ulcéreuse pneumococcique* Grandes hématemèses, in *Clinique médicale de l'Hôtel Dieu de Paris*, Paris, Masson & Cie, 1899, lesson 11, p 219, (c) footnote 2.

tions of the stomach, from pinpoint in size to 3 mm in diameter. These ulcers were located chiefly in the pylorus. Histologic and bacteriologic preparations showed pneumococci at the edge of the ulcer and in the surrounding interglandular connective tissue. In his second case no gross ulcerations were found, but there were microscopic hemorrhagic foci in the submucosa and interglandular tissue. Evidence of inflammatory reaction was absent, and organisms were not found. In Lorando's⁹ case the patient had a pyloric ulcer, whereas in the one reported by Griffon³ the patient had both pyloric and duodenal ulcers, but bacteria were not found. In the case of Sanford and his associates¹¹ the patient showed a large (4 cm) acute ulcer in the fundus with tiny ones nearby. Microscopic sections revealed an acute hemorrhagic reaction, bacteria were mentioned, but their identification was not recorded. In the case of the 28 month old baby described by Lesné, Heimann and Lièvre,⁸ no lesions were observed that could be justifiably considered the cause of the enterorrhagia. In the 5 cases in which there was ulceration, no microscopic evidence of chronicity or preexisting ulcer formation was noted.

Etiologic Agent.—The cause of the hemorrhagic manifestation has been attributed to the action of the pneumococci or their toxin on the endothelium of the capillaries, with resulting congestion, ulceration and hemorrhage. Dieulafoy,^{12a} cited the interesting experiment by Griffon and Bezançon in which the peritoneum of a guinea pig was inoculated with virulent pneumococci, which inoculation resulted in the production of petechiae in the mesentery and hemorrhagic ulcerations in the intestinal and gastric mucosae. Microscopic sections showed the mucosal and submucosal coats only were affected and the pneumococci were present in the ulcers, as in all organs. In only 2 of the autopsies cited, however, were bacteria noted at the site of the ulcer, and in only 1^{12a} was the pneumococcus identified. The pneumococcus was thought to be the causative agent in all cases except that described by Johnson,⁷ who termed the cause influenzal in nature. However, if one judges from his description, the influenza may have preceded the described lobar pneumonia. In his case and in all the others the pulmonary lesion was defined as lobar pneumonia, except in Chatard's case, in which pneumococcic empyema was considered to be the primary source of the pneumococcic infection. In only the 2 cases reported by Sanford and his associates¹¹ were the pneumococci successfully typed, and in both they were found to belong to type IV.

Treatment—Therapy in the reported cases has been that which is usually instituted for gastrointestinal bleeding and for shock, if present.

SUMMARY

A review of the literature on the intercurrentence of enterorrhagia in pneumonia reveals reports of but 23 cases, to which that of a new case is added. Analysis of these case reports has been made in regard to cause, age group, sex, occurrence of the hemorrhage, clinical manifestations, mortality and pathologic observations.

This condition now known as acute pneumococcic hemorrhagic ulcerative gastroenteritis, although not mentioned in recent American textbooks of medicine, is probably more common than the review of the literature reveals and should be considered as one of the more serious complications of lobar pneumonia.

Joseph H. Pratt Diagnostic Hospital

PLEUROPULMONARY TULAREMIA

STAIGE D BLACKFORD, M D

AND

CARLTON J CASEY, M D

UNIVERSITY, VA

The pleuropulmonary lesions associated with tularemia present such characteristic morphologic features that they must be accepted as a manifestation rather than a complication of the disease. These pathologic changes are frequent in persons with tularemia, and a variety of thoracic conditions may result clinically on account of their peculiar nature. These abnormalities in the chest may even obscure, and prevent the diagnosis of, the underlying tularemia. It is the purpose of this presentation (a) to review the salient morbid anatomic and pathophysiologic features of pleuropulmonary tularemia and (b) to analyze the clinical observations in a group of 95 unselected cases of tularemia with particular reference to abnormalities in the chest.

REVIEW OF PATHOLOGIC CHANGES

Because of duplications in the literature it is difficult to state exactly the number of reported cases of tularemia in which necropsy was done. Foshay¹ collected 43 necropsy reports but apparently failed to include 10 cases previously gathered by Lillie and Francis². Three other cases have been reported subsequently³. Thus it will be seen that there are probably 56 necropsy reports of tularemia on record. Lesions of tularemic pneumonia were described in 35 of these 56 autopsy records, indicating an incidence of 62.5 per cent in fatal cases.

From the Department of Internal Medicine, University of Virginia Hospital

1 Foshay, L. Cause of Death in Tularemia, Arch Int Med **60** 22-38 (July) 1937

2 Lillie, R. D., and Francis, E. The Pathology of Tularemia, Bulletin 167, National Institute of Health, February 1936, p. 76

3 (a) Pund, E. R., and Hatcher, M. B. Tularemic Meningitis. Report of a Case with Postmortem Observations, Ann Int Med **10** 1390-1398 (March) 1937. (b) Weilbaecher, J. O., Jr., and Moss, E. S. Tularemia Following Injury While Performing Postmortem Examination on Human Case, J Lab & Clin Med **24** 34-38 (Oct.) 1938. (c) Kimmelstiel, P., and Caldwell, H. W. Tularemic Septicemia. Report of a Case, Am J Path **15** 127-135 (Jan.) 1939

Two routes by which *Bacillus tularensis* may reach the lung have been discussed. Permar and MacLachlan⁴ and Fetterman and Leiner⁵ have suggested direct infection of the respiratory tract through inhalation and have presented illustrative cases in which cutaneous ulceration and regional adenopathy were lacking. On the other hand, Kavanaugh⁶ said that he considered hematogenous dissemination of the infection responsible for the pulmonary changes. The bacteremia known to occur early in many cases favors this view. Reimann⁷ has summarized the possibilities as follows:

In the general systemic form, the bacteria have a predilection for lymphoid tissue and produce granulomatous changes and later focal necrosis in the lymph nodes, spleen and lungs. In this form, the lungs are often invaded by way of the blood stream and pneumonia occurs as a concomitant localization. In the rare primary pulmonic form, as in plague, infection is apparently acquired by inhaling bacilli, suspended in air as dust or in droplets expelled from patients or animals who have tularemic pneumonia, or from handling dried cultures of the bacteria.

On the other hand, infection through inhalation has not been proved, and is extremely rare if it ever occurs. The failure to find a portal of entry does not mean that the organism entered through the respiratory tract. In the series being reported, ulcers or enlarged glands were found in one fifth of the patients with pneumonia, but in no instance was there reason to suspect inhalation of the organism. We feel that ulceration and adenopathy represent protective phenomena against massive systemic invasion and that when widespread visceral involvement occurs it is either because of an overwhelming inoculation or because of lack of protection, as manifested by the absence of ulcer formation and regional adenopathy. Visceral involvement which can be detected clinically (i. e., in the chest) is certainly relatively more frequent in patients with the so-called typhoid type of tularemia than in those with any other type of the disease.

The morbid anatomic features of tularemic pneumonia and tularemic hydrothorax have been comprehensively discussed by Lillie and Francis⁸ on the basis of 32 necropsies of the chest performed up to 1937. Addi-

4 Permar, H. H., and MacLachlan, W. W. G. Tularemic Pneumonia, *Ann Int Med* **5** 687-698 (Dec) 1931.

5 Fetterman, G. H., and Lerner, H. Fatal Case of Tularemic Pneumonia with Associated Ileitis. Clinical and Pathological Report, *J Lab & Clin Med* **21** 1157-1161 (Aug) 1936.

6 Kavanaugh, C. N. Tularemia. Consideration of One Hundred and Twenty-Three Cases with Observations at Autopsy in One, *Arch Int Med* **55** 61-85 (Jan) 1935.

7 Reimann, H. A. The Pneumonias, Philadelphia, W. B. Saunders Company, 1938, p. 277.

tional necropsy records have added little to their description of the pleuropulmonary pathologic changes in the disease, and their article has been freely drawn on for present purposes

In the thorax, as elsewhere, tularemia has been found to be primarily a necrotizing process, with foci of necrosis as the outstanding lesion. This fact differentiates tularemic pneumonia from pulmonary consolidation occurring in the course of certain other diseases as the result of secondary infection. Lillie and Francis stated

In fatal tularemia the most frequent pulmonary lesion is a pneumonia which is basically nodular or confluent nodular in character, sometimes lobar in extent, and involves from one to all lobes.²

The pleura has shown fibrinous, fibrinocellular and fibrinocaseous exudation in a number of cases

In order to understand the variable morphologic descriptions of pleuropulmonary tularemia, it is necessary to recognize that there are two pathologic processes going on simultaneously (*a*) a necrotizing action of the etiologic agent and (*b*) a cellular reaction of the reticulo-endothelial-monocytic-epithelioid type. In summarizing the pathologic process of tularemia in general, Lillie and Francis² remarked

In early lesions and those proximal to the primary lesions, necrosis tends to dominate and involves pre-existing fixed tissues as well as cellular exudates. Finally, old necrotic lesions become encapsulated, first by monocytes and epithelioid cells and later by fibrous tissue. Giant cells occur with appreciable frequency only in late lesions.

In reviewing the detailed pathologic descriptions reported it is necessary to bear in mind not only that the necrotizing action and cellular reaction are proceeding simultaneously with variable intensity but also that the duration of illness before necropsy varies in cases of human beings from a few days to many weeks.

The first reference to the peculiar histologic changes of pleuropulmonary tularemia was made by Verbrycke⁸ in 1924, when he described multiple areas of caseous necrosis surrounded by a zone of lymphocytes, with "bronchopneumonia" in adjacent alveoli and bronchioles and a pleural effusion of 100 cc, in a patient dying of tularemia. Bardon and Berdez,⁹ in 1928, observed whitish nodules on the pleura and distributed throughout the lungs, most densely in the areas of extensive bronchopneumonia. Shortly after this, Palmer and Hansmann¹⁰ noted "several alveoli and an occasional bronchiole filled with purulent

8 Verbrycke, J. R., Jr. Tularemia, with Report of a Fatal Case Simulating Cholangitis, with Postmortem Report, *J. A. M. A.* **82** 1577-1581 (May 17) 1924

9 Bardon, R., and Berdez, G. Tularemia. Report of Fatal Case with Postmortem Observations, *J. A. M. A.* **90** 1369-1371 (April 28) 1928

10 Palmer, H. D., and Hansmann, G. H. Tularemia. Report of a Fulminating Case with Necropsy, *J. A. M. A.* **91** 236-239 (July 28) 1928

exudate" in association with areas of marked congestion. In October 1928 Francis¹¹ first mentioned the frequency of bronchopneumonia as a terminal event in cases of tularemia, and Simpson¹² for the first time ascribed the physical signs of consolidation in his case to two areas of caseous necrosis resulting from tularemia rather than to nonspecific bronchopneumonia. Moreover, Bunker and Smith¹³ first recovered *B. tularensis* from the sputum. Autopsy in this case revealed consolidation containing a predominance of polymorphonuclear cells. In 1931, Masee¹⁴ reported a case of confluent pneumonia in which *B. tularensis* was recovered. He asserted that he had demonstrated an organism morphologically consistent with *B. tularensis* in the lung tissue, but Lillie and Francis² were unable to confirm this observation. Permar and MacLachlan⁴ described generalized areas of consolidation of a necrotic type which they called tularemic pneumonia, occurring most densely along the bronchial branches and interlobular septums. Monocytic cells predominated in the serous alveolar exudate. They expressed the opinion that necrosis had been produced by the extreme interstitial edema with monocytic infiltration and subsequent stenosis and thrombosis of venules and arterioles. Foulger, Glazer and Foshay,¹⁵ in 1932, reported numerous discrete and confluent caseous areas with necrosis and nuclear fragmentation, around many of which there were fibroblastic proliferation and a monocytic reaction. *B. tularensis* was said to have been stained in the lung tissue by a special technic. Blackford¹⁶ reported on the necropsy in a case of tularemia in which there was the clinical picture of an abscess of the lung, and he recorded the observation of a large cavity with vascular intimal proliferation and vascular thrombosis. In 1934, Gundry and Warner¹⁷ recorded the occurrence of a confluent consolidation with multiple localized foci of necrosis elsewhere. The exudate in this case was composed of lymphocytes, polymorphonuclear neutrophils and red blood cells. The caseation of the septums and alveolar contents resembled tuberculous pneumonia. In addition to the

11 Francis, E. Symptoms, Diagnosis and Pathology of Tularemia, *J. A. M. A.* **91** 1155-1161 (Oct. 20) 1928.

12 Simpson, W. M. Tularemia. Study of a Rapidly Fatal Case (Four Days, Seven Hours), *Arch. Path.* **6** 553-574 (Oct.) 1928.

13 Bunker, C. W. O., and Smith, E. E. Tularemia. Report of Four Cases, One Fatal, with Autopsy Report, *U. S. Nav. M. Bull.* **26** 901-911 (Oct.) 1928.

14 Masee, J. C. Tularemia in Georgia. Report of a Fatal Case, *J. M. A. Georgia* **20** 66-67 (Feb.) 1931.

15 Foulger, M., Glazer, A. M., and Foshay, L. Tularemia. Report of a Case, with Postmortem Examinations and a Note on the Staining of *Bacterium Tularensis* in Tissue Section, *J. A. M. A.* **98** 951-954 (March 19) 1932.

16 Blackford, S. D. Pulmonary Lesions in Human Tularemia. Pathologic Review and Report of a Fatal Case, *Ann. Int. Med.* **5** 1421-1426 (May) 1932.

17 Gundry, L. P., and Warner, C. G. Fatal Tularemia. Review of Autopsied Cases with Report of a Fatal Case, *Ann. Int. Med.* **7** 837-852 (June) 1934.

reports already cited, detailed descriptions of pleuopulmonary pathologic changes in cases of tularemia may be found in the reports of Goodpasture and House,¹⁸ Bryant and Hirsch,¹⁹ Hartman, Beaver and Green,²⁰ Gudger,²¹ Beck and Merkel,²² Sugden,²³ Bernstein,²⁴ Amoss and Sprunt,²⁵ and Stofel.²⁶

It can be seen from the foregoing anatomic descriptions that the fundamental lesion in the lung in persons with tularemia is focal necrosis either in the substance of the lung or in the pleura. The pneumonia appears to be characterized generally by predominance of monocytic cells in the exudate, but the exudate may also contain lymphocytes, red cells, plasma cells, desquamated epithelial cells and even polymorphonuclear neutrophils, which may indicate secondary infection of a pyogenic nature. Other features which may accompany the pneumonia are swelling of the epithelium lining the alveoli and congestion of the alveolar septums both in pneumonic and in unconsolidated areas. Interstitial infiltration is usually absent, but when present is most conspicuous in the interlobular septums and in the peribronchial and perivascular tissues. Vascular intimal proliferation plus mononuclear infiltration, thrombosis and necrosis with massive caseation have been described. The pleural lesions are characterized by focal necroses plus exudation.

The histologic resemblance of the initial focal necrosis in cases of tularemia to the early tubercles of tuberculosis has been pointed out by Kavanaugh⁶ and by Blackford²⁷ (figs 1 through 6). It would not be

18 Goodpasture, E. W., and House, S. J. Pathologic Anatomy of Tularemia in Man, *Am J Path* **4** 213-226 (May) 1928.

19 Bryant, A. R., and Hirsch, E. F. Tularemic Leptomenigitis. Report of Case, *Arch Path* **12** 917-923 (Dec) 1931.

20 Hartman, H. R., Beaver, D. C., and Green, R. G. Occurrence of Tularemia in Minnesota in 1921. Report of Two Cases, One Fatal with Necropsy Report, *Minnesota Med* **16** 559-566 (Sept) 1933.

21 Gudger, J. R. Tularemic Pneumonia. Report of a Case, *J A M A* **101** 1148-1150 (Oct 7) 1933.

22 Beck, H. G., and Merkel, W. C. Tularemia. Fatal Case of Typhoid Type Caused by Ingestion of a Rabbit, Autopsy Report, *South M J* **28** 422-428 (May) 1935.

23 Sugden, J. W. Tularemia, Deer Fly Fever. Report of Two Cases, One with Endocarditis, and Necropsy Findings, *Northwest Med* **34** 167-169 (May) 1935.

24 Bernstein, A. Tularemia. Report of Three Fatal Cases with Autopsies, *Arch Int Med* **56** 1117-1135 (Dec) 1935.

25 Amoss, H. L., and Sprunt, D. H. Tularemia. Review of Literature of Cases Contracted by Ingestion of Rabbit and Report of Additional Cases with a Necropsy, *J A M A* **106** 1078-1080 (March 28) 1936.

26 Stofel, D. D. Pericarditis with Effusion Complicating Tularemia, *Ann Int Med* **12** 407-412 (Sept) 1938.

27 Blackford, S. D. Similarities of Tularemia to Tuberculosis, *Tr Am Climat & Clin A* **53** 92-98, 1937.

surprising, therefore, to find analogous effects produced in the chest by these two diseases. The similarity of the pathologic process of the caseous pneumonia associated with tularemia to tuberculous pneumonia has been noted by Gundry and Warner,¹⁷ and Blackford and Archer²⁸ have pointed out a roentgenographic resemblance. The two conditions



Fig 1—Focus of necrosis of tularemia in a lymph node. The lesion shown in this figure should be compared with the tubercle of tuberculosis shown in figure 2. Figures 1 to 6 are presented by permission of Dr. Frank Foote, Jr.

are particularly likely to be confused clinically when they are accompanied by pleural effusion. As in tuberculosis, exudation into the pleural space in cases of tularemia may be a prominent feature. By the peri-

28 Blackford, S. D., and Archer, V. W. Roentgen Study of a Non-Fatal Case of Bilateral Tularemic Pneumonia Treated with Specific Serum, *J. A. M. A.* 109:264-265 (July 24) 1937.

bronchial infiltration already mentioned tularemia may cause bronchitis with subsequent peribronchial thickening visible on roentgen examination. More rarely, pneumothorax complicates tularemia. The exudate sometimes found in the lung in the acute stage of tularemic bronchitis may plug a bronchus, with resultant clinical atelectasis.

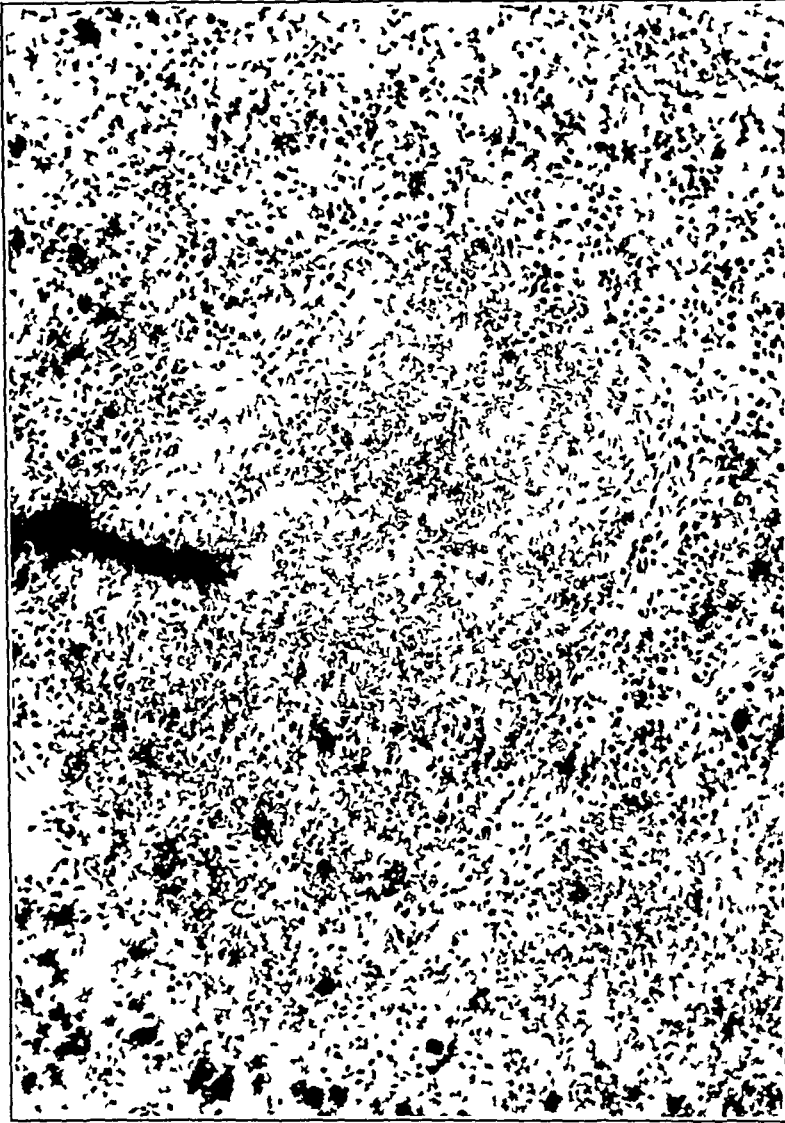


Fig 2—Tubercle in a lymph node

CLINICAL STUDY

In 1935, Blackford²⁹ and Archer, Blackford and Wissler³⁰ reported the clinical and roentgenologic findings in the cases of the first 35 patients

29 Blackford, S D. Pulmonary Manifestations in Human Tularemia. Clinical Study Based on Thirty-Five Unselected Cases, *J A M A* **104** 891-895 (March 16) 1935

30 Archer, V W, Blackford, S D, and Wissler, J E. Pulmonary Manifestations in Human Tularemia. A Roentgenologic Study Based on Thirty-Four Unselected Cases, *J A M A* **104** 895-899 (March 16) 1935

TABLE 1—Data on Cases of Tularemic Infection¹

Case	Sex	Race	Age, Year	Occupation	Type of Tularemia	Source of Inoculation	Incuba- tion, Days	Chief Complaint on Admission	Duration of Chief Complaint, Days	Initial Indication for Agglutination Test	Maximum Agglutina- tion Titer	B tularensis Present	Death	Autopsy
30	M	White	39	Road worker	UG	?	2	Glandular enlargement	14	Ulcer and glandular enlargement	1 40	—	—	—
37	F	Negro	26	Housewife	T	?	?	Vomiting	21	Fever	1 640	—	—	—
38	F	White	32	Housewife	G	Ticks ?	?	Sore throat	12	Fever	1 640	—	—	—
39	M	White	20	COO worker	G	?	?	Pain in side	1	Chest condition	1 320	—	—	—
40	M	Negro	43	Farmer	T	?	?	Hiccups	21	Chest condition	1 1,280	+	+	+
41	M	Negro	43	Gardener	T	Rabbit	4	Headache	14	Chest condition	1 1,280	—	—	—
42	M	White	28	Farmer	UG	Rabbit	3	Glandular enlargement	18	Glandular enlargement	1 1,280	—	—	—
43	M	White	27	Farmer—	UG	Rabbit	?	Glandular enlargement	28	Glandular enlargement	1 1,280	—	—	—
44	F	Negro	24	Housewife	UG	?	?	Glandular enlargement	90	Glandular enlargement	1 320	—	—	—
45	F	Negro	14	Student	UG	Rabbit	7	Ulcer	155	Ulcer and glandular enlargement	1 160	+	—	—
46	M	Negro	20	Farmer	UG	Rabbit	7	(Syphilis)	170	Ulcer and glandular enlargement	1 640	—	—	—
47	F	White	55	Housewife	UG	Rabbit	3	Ulcer and glandular enlargement	10	Ulcer and glandular enlargement	1 640	—	—	—
48	M	White	62	None	UG	Rabbit	1	Ulcer and glandular enlargement	21	Ulcer and glandular enlargement	1 160	—	—	—
49	M	White	11	Student	UG	Rabbit	?	Ulcer and glandular enlargement	42	Ulcer and glandular enlargement	1 640	—	—	—
50	M	White	28	Farmer	UG	Rabbit	?	Fluid in chest	120	Ulcer and glandular enlargement	1 1,280	+	—	—
51	F	White	53	Housewife	UG	Rabbit	?	Weakness	35	Ulcer and glandular enlargement	1 320	—	—	—
52	M	White	44	Farmer	T	Rabbit	?	Pneumonia	14	Chest condition	1 1,280	—	+	—
53	F	White	46	Housewife	UG	Rabbit	2	Skin eruption	12	Ulcer and glandular enlargement	1 1,280	—	—	—
54	F	Negro	25	None	UG	Rabbit	3?	Glandular enlargement	90	Ulcer and glandular enlargement	1 320	—	—	—
55	M	Negro	8	None	UG	?	7	Glandular enlargement	14	Ulcer and glandular enlargement	1 1,280	—	—	—
56	F	Negro	8	None	UG	?	?	Glandular enlargement	60	Ulcer and glandular enlargement	1 1,280	—	—	—
57	F	Negro	5	None	UG	?	?	Glandular enlargement	60	Ulcer and glandular enlargement	1 1,280	—	—	—
58	F	Negro	1½	None	UG	?	?	Glandular enlargement	60	Ulcer and glandular enlargement	1 1,280	—	—	—
59	M	White	42	Farmer	T	Rabbit	5	Chills	16	History	1 1,280	—	—	—
60	F	White	42	Housewife	UG	Rabbit	5	Glandular enlargement	3	Ulcer and glandular enlargement	1 320	—	—	—

61	M	Negro	9	None	G	Rabbit	9?	Coma	1	History	1 80	+	—
62	F	Negro	5	None	G	Rabbit	9?	Headache	4	History	1 5, 120	—	—
63	F	Negro	2	None	G	Rabbit	9?	Headache	1	History	1 1, 280	—	—
64	M	Negro	29	Farmer	UG	Rabbit	?	Ulcer	21	Ulcer and glandular enlargement	1 1, 280	—	—
65	F	White	47	Housewife	UG	Weasel bite	5	Glandular enlargement	480	History	1 640	—	—
66	F	White	40	Housewife	UG	Rabbit	1	Fever	10	History	1 640	—	—
67	M	Negro	24	Farmer	UG	Rabbit	1	Pain in chest	18	History	1 1, 280	—	—
68	M	White	28	Farmer	T	?	?	Skin eruption	6	Fever	1 1, 280	—	—
69	F	White	72	Housewife	UG	Rabbit	?	Glandular enlargement	42	History	1 1, 280	—	—
70	M	White	51	Farmer	T	?	?	Fever	14	Fever	1 800	—	—
71	M	White	17	Student	UG	Squirrel	?	Glandular enlargement	21	Glandular enlargement	1 1, 280	—	—
72	M	Negro	15	Student	UG	?	?	Glandular enlargement	21	Glandular enlargement	1 640	—	—
73	M	White	38	Laborer	T	Squirrel	?	Pain in chest	35	History	1 1, 280	+	—
74	F	Negro	21	Housewife	UG	Rabbit	?	Fever	14	Glandular enlargement	1 1, 280	—	—
75	M	Negro	13	None	OG	Rabbit	1	Abdominal cramps	3	Ocular trouble	1 1, 280	—	—
76	F	White	41	Housewife	UG	?	?	Glandular enlargement	9	Glandular enlargement	1 1, 280	—	—
77	M	White	48	Farmer	T	Ticks?	?	Fever	21	Chest condition	1 640	—	—
78	F	White	64	Housewife	UG	Rabbit	?	Glandular enlargement	14	Glandular enlargement	1 320	—	—
79	M	White	65	Farmer	UG	Rabbit	?	Glandular enlargement	14	Glandular enlargement	1 20	—	—
80	M	White	30	Mill worker	UG	Rabbit	4	Fever	14	History	1 1, 280	—	—
81	M	White	37	Farmer	G	Rabbit	?	Pneumonia	12	History	1 640	—	—
82	M	Negro	34	Laborer	UG	Rabbit	14	Glandular enlargement	150	Ulcer and glandular enlargement	1 1, 280	—	—
83	M	White	12	None	OG	Rabbit	5	Conjunctivitis	3	Fever and conjunctivitis	1 1, 280	—	—
84	M	White	31	Farmer	T	?	?	Fever	12	Fever	1 640	+	+
85	F	Negro	6	None	UG	Rabbit	2	Headache	4	Fever	1 320	+	+
86	F	White	35	Housewife	T	?	?	Weakness	90	Fever	1 1, 280	+	—
87	M	White	34	Farmer	UG	Rabbit	7	Ulcer and glandular enlargement	14	History	1 1, 280	—	—
88	M	White	9	None	UG	Cat	7	Ulcer	7	Fever	1 640	—	—
89	M	White	25	Laborer	T	Rabbit	5	Nosebleed	3	History	1 1, 280	—	—
90	M	White	19	Student	UG	?	14	Axillary pain	1	Glandular enlargement	1 1, 280	—	—
91	M	White	51	Farmer	UG	Rabbit	4	Fever and glandular enlargement	4	Ulcer and glandular enlargement	1 160	—	—
92	F	White	23	Housewife	UG	Rabbit	1	Ulcer and glandular enlargement	7	Ulcer and glandular enlargement	1 320	—	—
93	M	White	24	Farmer	UG	Rabbit	4	Ulcer	4	Ulcer	1 640	—	—
94	M	White	31	Laborer	T	Rabbit	16	Fever	14	History	1 640	—	—
95	M	White	19	None	UG	Rabbit	3	Fever	5	Ulcer and glandular enlargement	1 80	+	+

* Data on the first 35 cases of the series are given in Blackford 29

† The meanings of the abbreviations designating the type of tularemia are as follows UG, ulceroglandular, T, typhoid, G, glandular, and OG, oculoglandular

with tularemia observed at the University of Virginia Hospital. Since this report, 60 additional patients with the disease have been studied.

In the original publication,²⁹ the clinical data on the individual infections were tabulated, and table 1 of the present report submits similar data on the subsequent 60 patients. In the entire group, males outnumbered females approximately 2 to 1 and the ratio of white to

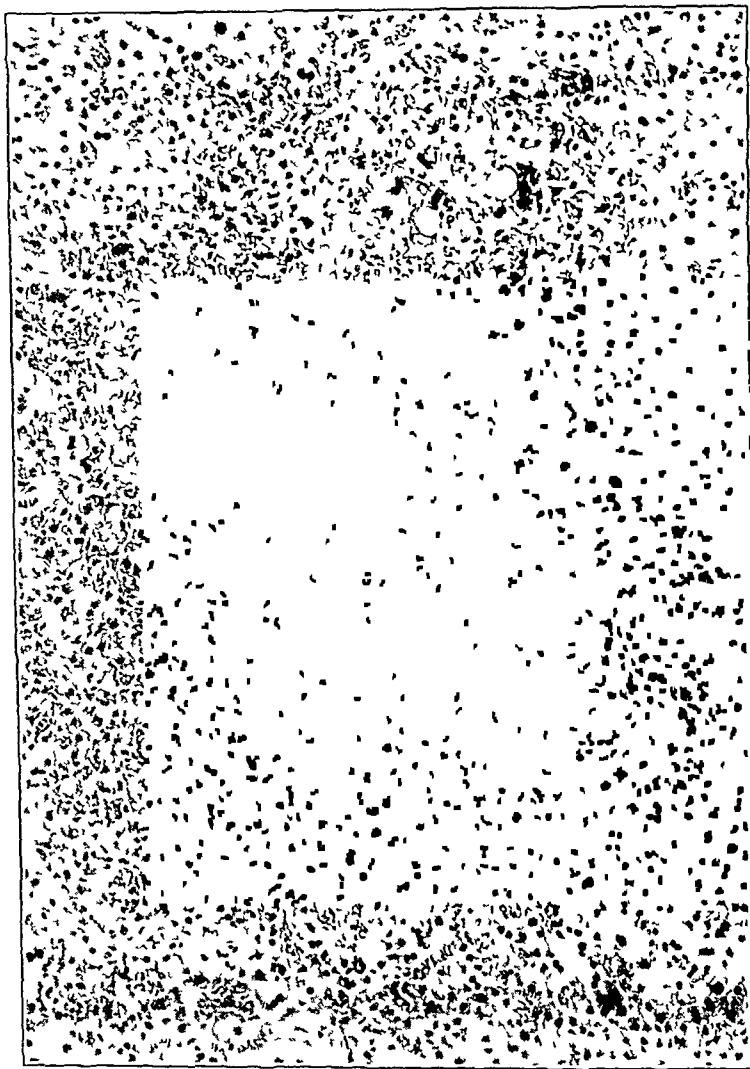


Fig. 3—Focus of necrosis of tularemia in the liver. The area of necrosis shown in this figure should be compared with the tubercle shown in figure 4.

Negro patients was likewise 2:1. All age groups were represented, 17 patients being less than 12 years old. A variety of occupations were listed, but more than half the patients were either farmers or housewives. The types of infection were grouped according to Francis' classification, as follows: ulceroglandular, 63 cases; typhoid, 21 cases; glandular, 7 cases; and oculoglandular, 4 cases. Whereas most of the inoculations were accounted for by rabbits, a few apparently resulted from contact with ticks, squirrels, opossums, weasels and cats. The periods of incuba-

tion seemed to vary from a few hours to two weeks. Ulcers or enlarged lymph nodes were the chief complaint of the majority of the patients, but the presenting symptoms covered a wide range. The patients were first seen from one day to several years after the onset of symptoms. The usual reason for obtaining an agglutination test for tularemia was the presence of ulcers or adenopathy, but many agglutination tests were



Fig 4—Tubercle in the liver

performed because of a suggestive history of contact, an unexplained fever or a chest condition of unknown cause. The diagnosis was confirmed by a positive agglutination reaction in all but 1 instance, in which *B. tularensis* was recovered post mortem. *B. tularensis* was recovered in 7 other cases. The mortality rate for the series was 10.5 per cent, and 7 necropsies were done in the 10 fatal cases.

In the former article,²⁹ the respiratory symptoms, physical signs and roentgen findings of the individual patients were also tabulated, and in

TABLE 2—*Respiratory Symptoms, Physical Signs and Roentgen Diagnosis in Cases of Tularemia*

Case	Respiratory Symptoms					Physical Signs				Roentgen Diagnosis						Number of Roentgenograms Taken		
	Cough	Sputum	Pain in Chest	Dyspnea	Interval Between Inoculation and Observation, Days	Signs, Days	Consolidation	Bronchitis	Pleural Fluid	Pleurisy or Exudation, Days	Interval Between Inoculation and Examination, Days	Pneumonia	Pleural Fluid	Excess Calcium	Nodular Infiltration		Abnormality Unexplained	Pneumothorax
36	2+	—	—	—	18	—	—	+	—	16	—	—	+	—	—	—	—	1
37	1+	1+	—	—	—	—	—	—	—	23	—	—	+	—	—	—	—	1
38	—	—	—	—	13	—	—	—	—	19	—	—	—	—	—	—	—	1
39†	3+	2+	3+	1+	14	+	+	+	+	8	—	—	—	—	—	—	—	3
40	3+	3+	3+	3+	21	+	+	+	+	25	—	—	—	—	—	—	—	2
41	3+	3+	2+	—	21	+	+	+	+	11	—	—	—	—	—	—	—	29
42	2+	1+	—	—	—	—	—	—	—	19	—	—	+	—	—	—	—	1
43	—	—	—	—	—	—	—	—	—	30	—	—	+	—	—	—	—	1
44	—	—	—	—	—	—	—	—	—	90	—	—	+	—	—	—	—	1
45	—	—	—	—	—	—	—	—	—	156	—	—	?	—	—	—	—	1
46	—	—	—	—	—	—	—	—	—	172	—	—	+	—	—	—	—	1
47	—	—	—	—	—	—	—	—	—	12	—	—	+	—	—	—	—	1
48	—	—	2+	2+	21	—	—	—	+	21	—	—	+	—	—	—	—	1
49	—	—	—	—	—	—	—	—	—	45	—	—	+	—	—	—	—	1
50	2+	—	2+	2+	120	—	—	—	+	120	—	—	+	—	—	—	—	1
51	—	—	—	—	—	—	—	—	—	38	—	—	+	—	—	—	—	1
52	3+	3+	—	3+	11	+	+	+	—	15	—	—	+	—	—	—	—	2
53	1+	—	1+	—	—	—	—	—	—	13	—	—	—	—	—	—	—	1
54	—	—	—	—	—	—	—	—	—	90	—	—	+	—	—	—	—	1
55	—	—	—	—	—	—	—	—	—	15	—	—	+	—	—	—	—	1
56	—	—	—	—	—	—	—	—	—	60	—	—	+	—	—	—	—	1
57	—	—	—	—	—	—	—	—	—	60	—	—	+	—	—	—	—	1
58	—	—	—	—	—	—	—	—	—	60	—	—	+	—	—	—	—	1
59	1+	—	—	—	16	—	—	—	+	17	—	—	—	—	—	—	—	2

this presentation table 2 offers the same material for the 60 new patients. Of the entire group of 95 patients, 40 had cough, 19 raised sputum, 19 had pain in the chest and 13 complained of dyspnea. Physical examination revealed signs suggesting consolidation in 23 patients, rales were recorded as occurring in 21, and signs indicative of pleurisy or pleural fluid were thought to be present in 16. One hundred and sixty-nine



Fig 5—Focus of necrosis of tularemia in the lung. The area of necrosis shown in this figure should be compared with the tubercle in figure 6.

roentgenograms of the chest were made in the study of 89 patients. Some type of roentgenographic abnormality was recorded as occurring in more than 90 per cent of this group.

A clinical diagnosis of tularemic pneumonia was made on the basis of physical signs or roentgen study for 20 of the 95 patients. Pleural fluid was removed from 13 patients, of whom 5 also had pneumonia. A diagnosis of bronchitis on the basis of symptoms, physical signs and roentgen study was justified in 19 instances, but the bronchitis was

uncomplicated in only 10 of these. In 1 of the 10 patients clinical atelectasis developed. It will be seen, therefore, that for 38 patients a clinical diagnosis of pleuropulmonary disease was warranted.

Pneumonia, hydrothorax and bronchitis will be discussed separately. Under each heading the American literature will be reviewed, the cases of this series discussed and a few cases of unusual interest presented.



Fig. 6—Tubercle in the lung

Pneumonia—Reports of 150 cases of tularemic pneumonia have been found in the American literature. In addition to references already given, reports of cases have been published by Sante,³¹ Tureen,³² Sloan,

31 Sante, L. R. Pulmonary Infection in Tularemia. Case Report, *Am J Roentgenol* **25** 241-242 (Feb.) 1931.

32 Tureen, L. L. Tularemic Pneumonia, *J A M A* **99** 1501-1502 (Oct. 29) 1932.

Freedburg and Ehrlich,³³ Massee,³⁴ Blumberg and Russell,³⁵ Boman and Bianco,³⁶ and Winter, Farrand and Herman³⁷ The three largest series are those of Foshay,¹ Kavanaugh⁶ and Blackford²⁷

The incidence of pneumonia in association with tularemia can be estimated only from the larger series In Foshay's¹ 400 cases of tularemia the incidence of pneumonia was 18.2 per cent Kavanaugh⁶ found that 12.7 per cent of his series of 123 patients had pneumonia, and the incidence in the present series was 21.5 per cent (table 3) As has been indicated, pneumonia occurs with greater relative frequency in association with the typhoid type of tularemia The type of tularemia was classified as ulceroglandular in 90 cases, typhoid in 51, oculoglandular in 4 and glandular in 3, and the type was not specified in 2 of the 150 cases of tularemic pneumonia found in the literature Foshay discovered pneumonia in 54 of his 351 patients with ulceroglandular tularemia and in 17 of his 32 patients with the typhoid type In the present series, 15 of the 21 patients with the typhoid form of the disease had pneumonia, and of the 20 with pneumonia 75 per cent had the typhoid type of tularemia

The symptoms of tularemic pneumonia are not characteristic The onset of such pneumonia is less abrupt than that of pneumococcic pneumonia, and it is often difficult to approximate the time of its onset from the symptoms alone Roentgen evidence of consolidation is first found from a few days to two weeks after tularemic inoculation The physical signs of pneumonia are nearly always present within three weeks of the onset of tularemic infection, and if they cannot be detected by this time it can be assumed that they will not occur later In the only instance in this series in which pneumonia was first noted more than three weeks after tularemic infection the patient (case 5 of the series) was admitted thirty-two days after the onset of tularemia, and at the time of admission he probably had had consolidation for more than ten days, for a large abscess of the lung was present

All of our patients with pneumonia presented respiratory symptoms at some stage of the illness, and cough, which was productive in half of the instances, was the most common symptom Pain in the chest and

33 Sloan, L. H., Freedburg, A. S., and Ehrlich, J. C. Tularemic Pneumonia, *J. A. M. A.* **107** 117-119 (July 11) 1936

34 Massee, J. C. Tularemic Studies in Georgia, *J. M. A. Georgia* **21** 7-12 (Jan) 1932

35 Blumberg, A., and Russell, R. L. Intrathoracic Changes in Tularemia, *South. M. J.* **27** 578-583 (July) 1934

36 Boman, P. G., and Bianco, A. J. Tularemic Pneumonia, *Ann. Int. Med.* **7** 1491-1495 (June) 1934

37 Winter, M. D., Farrand, B. C., and Herman, H. J. Tularemia, Pulmonic Form. Report of Four Recoveries, *J. A. M. A.* **109** 258-262 (July 24) 1937

TABLE 3—*Tularemic Pneumonia (Twenty Cases)*

Series No	Type of Tular-emia	Indication for Agglutination Test	Average Pulse Rate	Maximum Temperature, F	Maximum White Blood Cell Count	Respiratory Symptoms				Days After Infection			Respiratory Signs				Roentgen Signs			Death	Autopsy
						Cough	Sputum	Pain	Dyspnea	After	Consoli- dation	Bron- chitis	Pleural Fluid	Conso- lidation	Necrosis						
1	T	Fever	96	101.6	12,500	1+	0	3+	0	16	+	0	?	+	0						
2	T	Fever	100	101	11,200	2+	1+	3+	1+	1	+	+	+	+	0						
5	T	Fever	110	105	8,500	3+	3+	0	0	32	+	0	0	+	+	+				+	
10	G	Biopsy	100	105	9,000	1+	0	0	0	2	+	+	0	+	?						
26	T	Fever	100	106	9,200	3+	1+	2+	0	6	+	+	+	+	+	+				+	
28	T	Chest condition	90	101	7,200	2+	1+	2+	0	8	+	+	?	+	0						
30	T	Fever	90	101	11,400	1+	0	0	0	5	+	0	0	+	0						
31	UG	Glandular enlargement	100	107	10,000	1+	0	0	0	8	+	+	0	+	+	+				+	
40	T	Chest condition	120	106	7,000	3+	3+	3+	3+	21	+	+	+	+	0					+	
41	T	Chest condition	110	104	8,000	3+	3+	2+	0	21	+	+	0	+	0						
52	T	Chest condition	110	106	10,800	3+	3+	0	3+	11	+	+	0	+	+	+				+	
70	T	History	100	104	12,800	1+	0	0	0	18	+	0	+	+	0						
66	UG	History	90	103	11,500	2+	2+	3+	2+	11	+	+	0	+	0						
67	UG	Glandular enlargement	90	102	12,600	2+	0	3+	0	18	+	+	0	+	?						
77	T	Chest condition	90	103	12,400	2+	0	2+	2+	7	+	0	+	+	0						
80	T	Chest condition	110	104.6	5,400	3+	1+	2+	0	11	+	0	0	+	0						
84	T	Fever	120	105	13,800	1+	1+	0	3+	12	+	0	+	+	0					+	
89	T	History	90	103	7,400	0	0	2+	0	20	+	0	0	+	0						
94	T	History	90	102.8	10,200	1+	0	0	0		0	0	0	+	0						
95	UG	Ulcer	90	105.8	25,600	1+	0	0	0	17	+	0	0	+	0					+	

dyspnea occurred frequently. One patient had only pain in the chest, without cough or dyspnea. In general, the pulse was slow and the leukocyte count low with reference to the fever. In the group with pneumonia, with the exception of the patient in case 94, only those patients were included who had both physical and roentgen evidence of pulmonary consolidation. On physical examination, many of these patients had signs of bronchitis elsewhere in the lungs and one fourth of them also presented physical signs of pleural fluid. On roentgen examination 4 patients had in addition definite evidence of necrosis, and all 4 of these died. In 2 instances, in which the presence of necrosis of the lungs could not be definitely determined on the basis of roentgenograms of the chest, the patients survived.

The duration of the illness was variable. In 1 instance all roentgen evidence of consolidation had disappeared within ten days of its appearance, but in another consolidation was seen in roentgenograms of the chest six weeks after it was first noted and four weeks after the patient had been afebrile. In general high fever usually persisted from two to four weeks, but recovery of normal strength was ordinarily a matter of many months. Recently 1 patient has returned with severe acute pleurisy, thirty months after pneumonia. Although a roentgenogram of the chest made after discharge from the hospital was normal, the patient asserts that he has never recovered his strength sufficiently to work, and at present he has roentgen evidence of pleurisy.

It has been mentioned that 62.5 per cent of patients with tularemia who die have pneumonia. On the other hand, tularemic pneumonia is not as fatal a disease as one might believe. It is true that the mortality rate is considerably higher among those patients having tularemia with pneumonia than among those having tularemia without pneumonia, but Foshay¹ stated the belief that 70 per cent of patients with tularemic pneumonia survive, and in this series 65 per cent of the patients with pneumonia recovered. Thus the mortality rate in routine cases of tularemic pneumonia is probably about 30 per cent. A survey of the literature might lead one to expect a higher mortality rate, for most of the recorded cases are reported for the necropsy data. Perhaps another factor to suggest an extremely high mortality rate is that unless roentgenograms of the chest are made routinely, the presence of pneumonia is detected only in the patients with tularemia who are most seriously ill. Conversely, it is likely that many patients die of tularemic pneumonia without the benefit of a diagnosis of tularemia, for the disease may be fatal before the reaction to the agglutination test becomes positive. This happened in the case of 1 of our patients. Foshay¹ expressed the belief that the pneumonia per se is not the cause of death but that septicemia is "the chief cause of death attributable to tularemia alone," and that the higher fatality rate of tularemic pneumonia is attributable to the fact that pneumonia is evidence for primary septicemia.

Of our 5 cases of pneumonia in which necropsy was done 2 have been reported elsewhere³⁸ Three previously unrecorded cases of fatal pneumonia in which necropsy was performed are briefly presented here

REPORT OF CASES

CASE 40—A 43 year old Negro farmer had sharp inspiratory pain in the left side of the chest, followed immediately by a severe chill and later by frequent drenching night sweats, two weeks before being admitted to the hospital on Sept 6, 1934 Three days before his entrance severe hiccup appeared No other respiratory symptoms were present

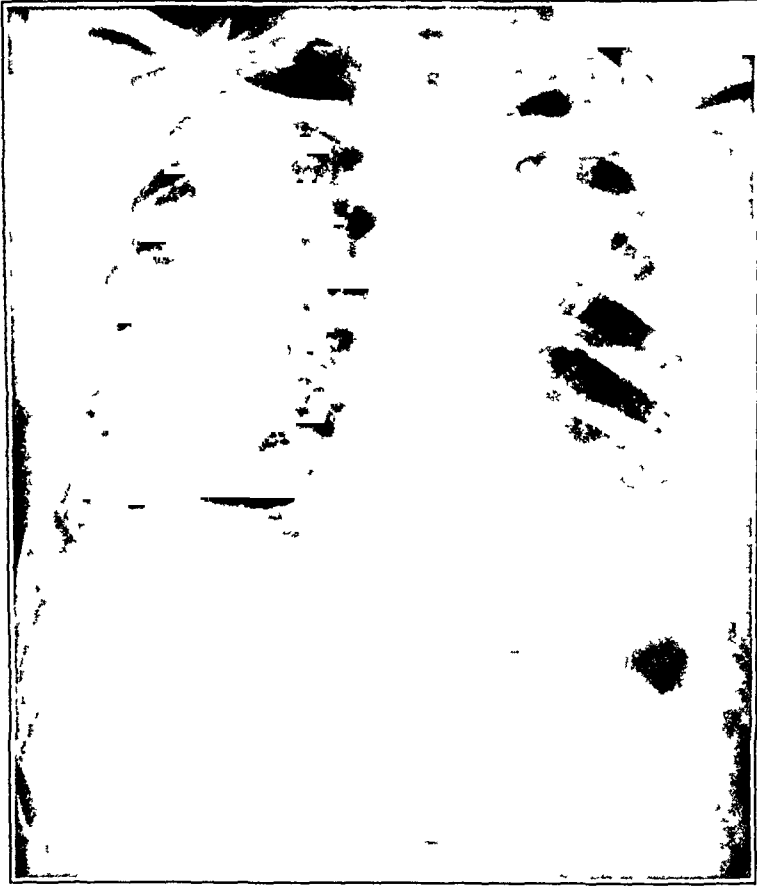


Fig 7—Central consolidation and fluid at the base of the left lung

The temperature on admission was 104.4 F, and examination elicited signs of fluid in the left side of the chest Thoracentesis at the time yielded 500 cc of a greenish yellow fluid, with 456 cells, equally distributed between polymorphonuclear neutrophils and lymphocytes The blood agglutinated *B. tularensis* in a dilution of 1:1,280, and the fluid from the chest, removed on September 10, gave a positive reaction in the same dilution *B. tularensis* was recovered from the fluid from the chest by means of guinea pig inoculation

Roentgen examination of the chest on September 10 showed an area of central consolidation in the left lung and fluid in the base of the left lung (fig 7) Four

38 Blackford (footnotes 16 and 29)

days later the consolidation in the left lung was less extensive and an additional area of consolidation was detected in the right lung. The patient's condition progressively became worse, and he died on September 16.

Necropsy—The left pleural cavity was practically obliterated anteriorly and laterally by recently organized fibrous adhesions. The right pleural cavity was entirely obliterated by older fibrous adhesions. An area of consolidation, about 3 cm in diameter, was present in the apex of the left lung, with multiple smaller consolidated areas throughout the remainder of the upper lobe of the left lung. An area of lobular consolidation, about 8 cm in diameter, was found in the upper lobe of the right lung, and many smaller areas were scattered throughout the middle and the lower lobe. Microscopically, some areas revealed predominance of polymorphonuclear and others of large mononuclear cells. Necrosis was marked in many sections. The similarity to tuberculous pneumonia was pronounced in some zones. Focal necroses appeared in the liver and spleen. There was a large hemorrhage in the diaphragm.

CASE 84—A white man aged 31 entered the hospital on July 16, 1939, giving a history of generalized abdominal pain, slight headache and sore throat, with chilly sensations of twelve days' duration. He had been feverish and semicomatose for five days. There was a history of exposure to ticks, and an agglutination test for Rocky Mountain spotted fever had been reported as giving a positive result in dilution of 1:20 two days before admission.

Examination disclosed a semicomatose young white man with a temperature of 105 F and a pulse rate of 120. The neck was slightly stiff and the throat acutely inflamed. Slight dullness and suppression of the breath sounds, with a few fine rales, were present in the base of the right lung posteriorly. The next day physical signs of consolidation were prominent. The roentgenographic report described the consolidation as atypical. On July 19 thoracentesis on the right side yielded 750 cc of cloudy yellow fluid, the procedure was repeated on the following day, with the removal of 400 cc of similar fluid. The patient's condition remained critical, and he died on July 20.

The only significant laboratory findings were positive agglutinations for *B. tularensis* with the fluid from the chest in a dilution of 1:320, and with the blood in a dilution of 1:640 on the day of death.

Necropsy—There was widespread confluent lobular pneumonia of both lungs, more marked on the right. The consolidated areas were patchy and showed numerous areas of necrosis. The alveoli in the intervening areas were filled with an exudate containing fibrin, blood, a few polymorphonuclear neutrophils and many round cells, principally mononuclears. In these areas, considerable endothelial hyperplasia of the capillaries in the alveolar walls was present, the vessels being greatly narrowed. There was a mass of inflammatory necrotic glands surrounding the trachea and primary bronchi. The right pleural cavity contained 150 cc of thin cloudy fluid and the left 200 cc. The liver, spleen, adrenal glands and mesenteric lymph nodes showed focal necroses.

CASE 95—A 19 year old white man dressed several rabbits on Nov. 24 and 26, 1939 and on Nov. 27 had a severe frontal headache and became feverish. Tender epitrochlear and axillary lymph nodes appeared two days afterward, and later a mild nonproductive cough. He had had a crusted wound on the middle finger of the right hand for the preceding month.

Significant physical findings on admission, December 1, in addition to the wound and lymphadenopathy, included moist rales, bronchovesicular breath sounds and increased whispered voice conduction over the base of the left lung. The tempera-

ture was 103.4 F. On December 8 consolidation was prominent on the left, and on December 10 it was found in the right lung also. The patient's condition became progressively worse, and he died on December 11. Administration of anti-tularensis serum and of sulfapyridine did not alter the course of the illness. The maximum titer in which positive agglutination for *B. tularensis* was obtained was 1:80, on the ninth day.

Necropsy.—Both lungs presented many nodular areas distributed throughout the substance, which on the cut surface disclosed necrosis. Microscopically these areas showed a central area of caseous necrosis in which a coagulated structureless material was filled with pyknotic nuclear fragments. Surrounding the circumscribed areas were zones of coagulation in which the structure of the lung was still discernible, but the alveoli were filled with coagulated exudate bearing many cells, among which large and small mononuclears predominated. At the margin of the necrotic zone there was a scanty proliferation of epithelioid cells. Elsewhere acute ulcerative bronchitis with considerable peribronchial infiltration and small areas of lobular pneumonia and multiple areas of atelectasis was noted. The liver and spleen showed widespread focal necroses.

Hydrothorax.—Of the 32 cases collected by Lillie and Francis² in which the patient died, pleural exudates were noted in 16 and focal nodular lesions were found in the pleura in 1 other. Lewy,³⁹ Weilbaecher and Moss^{3b} and Stofel⁴⁰ have reported additional fatal cases in which the patient had pleural effusion. Pleural effusions in cases of tularemia in which the patient survived have been recorded by Masee,³⁴ Blumberg and Russell,³⁵ Kavanaugh,⁶ Warring and Cullen⁴⁰ and Blackford.²⁷ Pleural exudation in cases of tularemia in which death did or did not occur has, according to reports in the literature, been found in less than 30 cases, exclusive of the 13 in the present series.

The incidence of hydrothorax in association with tularemia is unsettled. Foshay¹ made no mention of pleural exudation. Kavanaugh⁶ noted its presence only three times in his series. On the other hand, pleural fluid was obtained from 13 of our 95 patients, an incidence of 13.7 per cent. In 5 of these 13 patients pleural effusion was associated with pulmonary consolidation and in 1 with a "round focus" simulating tuberculosis. In almost all instances the hydrothorax was of clinical importance in its own right, and in several cases the presence of the pleural fluid gave the first indication of the diagnosis of tularemia.

According to our experience (table 4) hydrothorax is more likely to be encountered in association with the typhoid type of tularemia, 9 of the 21 patients with the typhoid type presenting pleural effusion. Of the 13 patients with pleural effusion 69 per cent had the typhoid type of tularemia.

39 Lewy, R. B. Pulmonary Tularemia. Report of a Case with Necropsy, *Illinois M. J.* **70** 192-193 (Aug.) 1936.

40 Warring, F. C., Jr., and Cullen, V. F. Tularemia with Pleural Effusion. Case in Which Bacterium *Tularensis* Was Isolated from Pleural Fluid During Life, *J. A. M. A.* **107** 1365-1367 (Oct. 24) 1936.

TABLE 4—*Tularemia Pleural Effusion (Thirteen Cases)*

Series No	Type of Tularemia	Indication for Agglutination Test	Average Pulse Rate	Maximum Temperature, F	Respiratory Symptoms				Pleural Fluid										Death	Autopsy
					Maximum White Blood Cell Count	Cough	Sputum	Pain	Dyspnea	Weeks After Infection	Total Amount of Fluid Removed, Cc	Specific Gravity	Total No of Cells	Per Cent of Polymor- phonuclears	Per Cent of Lymphocytes	Agglutina- tion Titer	Acid Fast Organism	Guinea Pig Inoculation		
2*	T	Fever	100	104	11,200	2+	1+	3+	1+	2	860	1 021	3,100	4	96	1 1,280	0	G P lost		
12	UG	Glandular enlargement	90	101	8,000	1+	0	1+	1+	9	400	1 022	3,100	7	93	1 1,280				
20*	T	Fever	100	106	9,200	3+	1+	2+	0		Fluid at autopsy not studied									
35	T	Chest con- dition	90	102	7,700	2+	0	3+	3+	16	1,100	1 027	240	Occa- sional		1 80	0	G P died, 6 days	+	+
40*	T	Chest con- dition	120	104	7,000	3+	3+	3+	3+	4	630	1 020	3,100	22	78	1 1,280	0		+	+
50	LG	Glandular enlargement	85	100	11,000	2+	0	2+	2+	12	550	1 023	750	3	97		0	B tular- ensis	+	
59	T	History	100	104	12,800	1+	0	0	0	3	100						0	Negative for tubercle bacillus		
69	UG	Glandular enlargement	110	100		0	0	0	0	7	275	1 020	9,400	Lymphocytes predominant		1 1,280	0			
77*	T	Chest con- dition	90	103	12,400	2+	0	2+	2+	?	2,600	1 017	7,000	Lymphocytes predominant		1 320	0	G P died, 9 days		
78	T	Chest con- dition	130	103 6	19,800	2+	2+	3+	3+	6	3,650	1 020	13,000	94	6	1 1,280	0	G P died, tularemi- a		
81	G	History	85	102 4	10,200	2+	0	3+	0	?	800	1 019	920	6	94	1 640	0			
84*	T	Fever	120	105	13,800	1+	1+	0	?	2	1,150		1,270	76	24	1 320	0		+	+
86	T	Fever	100	103	13,800	0	0	0	0	12	500+?	?	4,710	23	77	1 1,280	0	G P died, 3 days, tularemia		

* Included in table 3 also

Pleural effusion appears to occur somewhat later after tularemic inoculation than does pneumonia. Pleural fluid was not detected within the first two weeks in this series, and in the majority of cases four weeks or more elapsed before its accumulation. In 3 instances fluid was removed more than three months after tularemic infection. In general, the symptoms encountered were comparable with those found accompanying tuberculous effusions, with the exception of a relatively slow pulse rate. High fever was noted only in those patients who had associated pneumonia. Usually the leukocyte count was normal or only slightly elevated.

In this group only those patients were included from whom pleural fluid was actually removed. The presence of the fluid was suggested by either physical or roentgen signs in several additional instances. The total amount of fluid aspirated varied from 100 to 3,650 cc, but usually the thoracenteses were performed for therapeutic as well as diagnostic purposes. All the specific gravities were above 1.017, indicating exudation rather than transudation. The color was usually yellow, with little or no cloudiness. Total cell counts of more than 10,000 per hundred cubic millimeters were exceptional. Almost invariably lymphocytes predominated over polymorphonuclear neutrophils in the exudate. All the fluids tested agglutinated *B. tularensis*, generally in the same dilutions as the bloods of the respective patients. All stains for acid-fast organisms were negative. In 3 instances inoculation of guinea pigs with the fluid withdrawn produced death from tularemia, and in 2 other instances death resulted in a few days, presumably from tularemia. Three of the 13 patients died, but all 3 of these also had tularemic pneumonia, which was the probable cause of death. Probably tularemic pleural effusion alone is rarely fatal.

Pneumothorax in association with tularemic pleural effusion appears to be a relatively rare complication. Kavanaugh⁶ mentioned 1 case in which the patient died of spontaneous pneumothorax on the thirteenth day of illness, and Blackford²⁹ previously reported briefly a similar fatal case in this series (case 26). The patient in our second case of pneumothorax survived, and since only 1 other case in which the patient survived has been recorded³³ in the literature, we present this case in some detail.

CASE 73—A white man aged 38 complained on admission, Dec. 1, 1938, of sharp pain in the left side of the chest, of increasing severity, which radiated to the left axilla and was associated with a dry cough and dyspnea, of one day's duration. He gave a history of skinning a squirrel seven weeks previously and of having a week later an acute illness, characterized by slight fever, general malaise, sore throat, mildly productive cough and pain in the left portion of the chest, which was aggravated by respiration.

Physical examination revealed an acutely ill, dyspneic man, with a temperature of 103 F, a pulse rate of 132 and a respiratory rate of 40. Physical findings were

typical of hydropneumothorax on the left. Roentgen examination (fig 8) confirmed these findings and showed a marked inflammatory reaction in both pulmonary fields, extending from the apex to the base on the right and infiltrating the central portion on the left. Agglutination reactions of the blood serum for *B. tularensis* five to eight days later were positive in a dilution of 1:1,280.

Thoracentesis on admission yielded 350 cc of straw-colored, slightly cloudy fluid, with a total cell count of 13,150, of which 94 per cent were polymorphonuclear neutrophils. Stain for acid-fast organisms revealed no tubercle bacilli. A guinea pig inoculated with fluid from the chest died on the eighth day, and gram-negative bacilli thought to be *B. tularensis* were found in foci of necrosis in the viscera. Subsequent thoracenteses produced 1,350 cc on one occasion and 350 cc on another, both specimens having cell counts comparable with the first. Fluid removed by the second tap gave a negative agglutination reaction for *B. tularensis*, but that taken by the third tap gave a positive reaction in a dilution of 1:1,280.



Fig 8—Hydropneumothorax on the left side with marked inflammatory reaction in both lungs and central infiltration of the left lung. A, anteroposterior, and B, lateral, view.

The temperature remained at practically the same level for eleven days, with the pulse correspondingly increased. Partial relief of the patient's discomfort was obtained by thoracentesis. He was discharged from the hospital on December 15 and instructed to remain in bed at home for two weeks.

He returned on Jan 12, 1939, stating that his pain had been minimal until two weeks previously, when, on his getting out of bed, it had recurred in its former intensity, with progressive dyspnea. He had raised a small amount of sputum. Results of physical examination of the chest were practically identical with those seen on the first admission. Roentgenograms of the chest showed that the left lung was completely collapsed and that hydropneumothorax occupied the left thoracic cage. Thirteen hundred cubic centimeters of fluid was aspirated. Agglutination tests of the blood and fluid from the chest for *B. tularensis* were repeated, and those of both gave positive reactions in dilutions of 1:1,280.

The patient's condition on subsequent visits to the clinic was improved. On one visit 400 cc of thinly purulent material was removed from the left side of the

chest Four days later fluoroscopic procedure revealed only a small amount of fluid estimated at 100 cc Results of roentgen examination of this patient's chest in July 1940 were essentially normal

Comment—It seems likely that the pneumothorax in this case resulted from a ruptured focal abscess, as described by Kavanaugh⁶ However, it is conceivable that fibrosis from tularemia may cause a ball valve action, with cyst formation and subsequent rupture Cystic disease of the lung was found in another patient (case 81), but under the circumstances it was impossible to say whether the cysts resulted from tularemia or antedated its onset

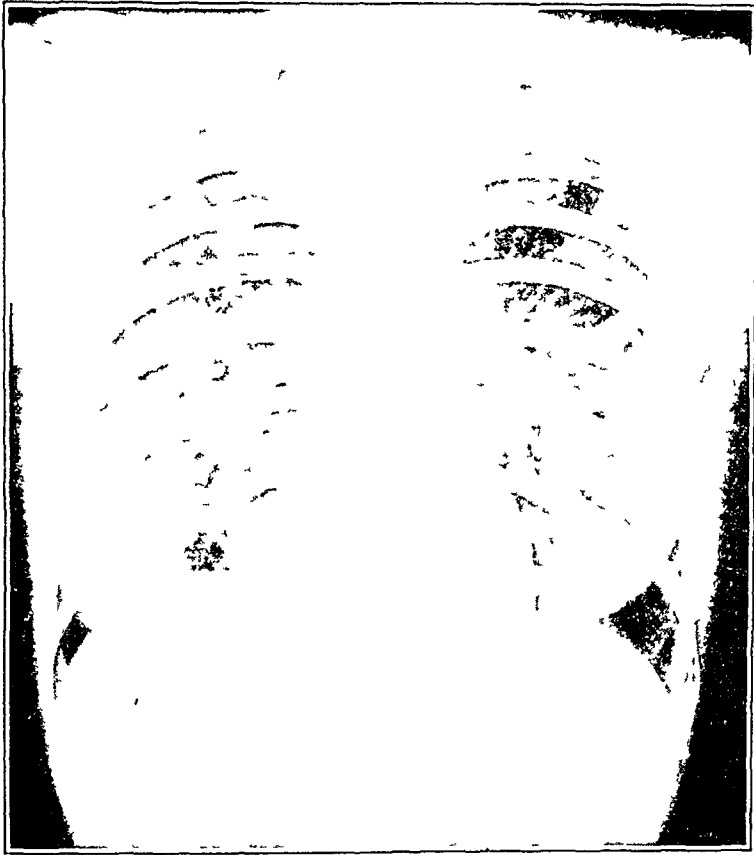


Fig 9—Round focus simulating tuberculosis in the left lung

In 1 of the most recent cases in which pleural effusion occurred there was such an interesting differential diagnosis between tularemia and tuberculosis that we record it here

CASE 86—A white married woman aged 35 entered the hospital on Aug 2, 1939 with the complaint of loss of weight and headache for several months One week prior to her admission she had fever for several days, together with frequency of urination, dysuria and generalized aching She gave a history of four attacks of atrophic arthritis There was a history of tuberculosis in the family Physical examination and routine laboratory studies contributed no significant information

Roentgen examination of the chest on August 4 (fig 9) showed the left lung to contain a round dense area, 1.5 cm in diameter, surrounding which was a

TABLE 5—*Uncomplicated Clinical Brucellosis (Ten Cases)*

Series Number	Type of Tularemia	Indication for Agglutination Test	Average Pulse Rate	Maximum Temperature, F	Maximum White Blood Cell Count	Respiratory Symptoms			Day Rains Noted After Infection
						Cough	Sputum	Pain	
3	UG	History	90	101.1	11,500	2+	2+	0	11
1	UG	Ulcer and glandular enlargement	85	100.6	5,000	2+	0	0	37
6	UG	Ulcer and glandular enlargement			8,500	2+	0	0	19
11	UG	Ulcer and glandular enlargement				2+	2+	0	900
19	UG	Ulcer and glandular enlargement				2+	1+	0	18
23	UG	Ulcer and glandular enlargement				2+	1+	0	6
25	UG	Ulcer and glandular enlargement				1+	0	0	10
36	UG	Ulcer and glandular enlargement	90	101.6	12,100	2+	0	0	18
70	T	Fever	100	101.8	12,000	1+	0	0	
91	UG	Ulcer	80	103.2	13,200	1+	0	0	11

small spotted soft infiltration. Many discrete areas of calcium deposit were present in the right lung. The findings were interpreted as representing the so-called round focus of tuberculosis. Tests of a specimen of sputum for acid-fast bacilli gave negative results.

On the day of the roentgen examination, results of agglutination tests of the blood serum for *B. tularensis* were positive in a dilution of 1:20. Four subsequent agglutination tests gave positive results in a dilution of 1:1,280.

Presumptive diagnosis of pulmonary tuberculosis having been made, artificial pneumothorax was instituted five days after the patient's entrance to the hospital, and fluoroscopic examination revealed a trace of fluid in the base of the left lung. Seven days later the amount of fluid had increased. Studies of the fluid on August 18 showed positive agglutination for *B. tularensis* in a dilution of 1:1,280 and no acid-fast bacilli. A guinea pig was inoculated with the fluid and died three days afterward. *B. tularensis* was cultured from the tissues of the animal, and microscopic sections revealed lesions consistent with *B. tularensis*.

The patient was transferred from the hospital on August 19 to a sanatorium for tuberculous patients, where she remained for three months, receiving treatment by artificial pneumothorax. On admission intradermal injection of tuberculin gave a 4 plus reaction. She gained weight, and her condition progressively improved.

Comment—Whether the process was primarily of tularemia or of tuberculous origin, or whether the two conditions were coexistent has been a matter of considerable dispute. Undoubtedly this patient had an active tularemia infection, which was proved by recovery of the organism, and we believe that it is unnecessary to assume tuberculous activity to account for the findings in the chest.

Bronchitis—No reference to the occurrence of bronchitis in association with tularemia has been found except for the previous reports⁴¹ published about the earlier cases in this series. Of our first 35 patients clinical bronchitis, manifested by cough and rales in the chest, was detected in 12, and in 7 of these the condition was independent of other involvement of the respiratory tract. Among the remaining 60 patients in the present series bronchitis was relatively less frequent, there being only 7 patients with bronchitis, in 3 of whom the condition was uncomplicated. Thus, of the 95 patients clinical bronchitis was detected in 19. The bronchitis was uncomplicated in 10 patients (table 5). On the other hand, peribronchial thickening visible roentgenographically was frequent, occurring in 51 of the 95 patients.

Of course it is difficult to prove that the clinical bronchitis and the peribronchial thickening noted in these patients resulted from tularemia. However, the fact that bronchitis has been observed at necropsy in persons with tularemia and that bronchitis was found so frequently in this series makes it logical to attribute this condition to the tularemia infection.

41 (a) Blackford²⁹ (b) Archer, Blackford and Wissler³⁰

As has been pointed out previously,²⁹ the prognosis is not serious when bronchitis alone is present, and patients with uncomplicated bronchitis are usually no more seriously ill than those without clinical indications of involvement of the respiratory tract. Chronic bronchitis of clinical significance may ensue, but it has occurred rarely in the patients we have encountered. However, roentgen studies of this series indicate that peribronchial thickening may persist for years.

Massive atelectasis during life has not been mentioned, although several autopsy reports record small areas. In the case here presented, the atelectasis apparently resulted from excessive bronchial exudate and was relieved by bronchoscopic drainage.



Fig 10—Atelectasis of the middle lobe of the right lung and semiconsolidation of the upper lobe of the right lung, *A*, anteroposterior, and *B*, lateral, view

CASE 7—A white farmer aged 51 was admitted to the hospital on Oct 10 1938, with a history of generalized malaise and aching, high fever, dry nonproductive cough and delirium for the preceding two weeks. Three days before his entrance results of agglutination tests of the blood for *Bacillus abortus* and *B. tularensis* were negative.

On admission the patient appeared acutely ill. The temperature was 99 F, the pulse rate 88 and the respiratory rate 20. The physical findings over the right side of the chest suggested pneumonia at the base of the upper lobe and pneumonia or atelectasis of the middle lobe. Results of neurologic examination were negative. Agglutination tests of the blood revealed *B. tularensis* in a dilution of 1:640 on October 14 and in a dilution of 1:1,280 four days later. Examination of the sputum gave negative results.

The day after entrance the temperature rose to 104.2 F and remained elevated. No cough or sputum was present. Roentgen examination (fig 10) revealed atelectasis of the middle lobe and semiconsolidation of the lower lobe of the right lung. On October 12 bronchoscopic examination disclosed considerable straw-

colored fluid and a coagulated mass of serum in the bronchus to the lower lobe of the right lung, and this mass was aspirated. The bronchus to the middle lobe was patent, and more of the straw-colored fluid was aspirated by introduction of a curved tube. After bronchoscopy the cough became more productive. The temperature progressively declined on the succeeding three days and continued at normal levels thereafter. On the patient's discharge from the hospital, on October 24, his condition was improved.

COMMENT

The pleuropulmonary pathologic process associated with tularemia is of interest to the student of the disease, but more important to the clinician is the fact that these nodular lesions, which are histologically similar to tubercles, may produce during the life of the patient a variety of thoracic conditions easily confused with pulmonary tuberculosis. Caseous pneumonia, pulmonary cavitation, nonpurulent pleural effusion, spontaneous pneumothorax, a lesion resembling a "round focus" of tuberculosis and bronchitis have been detected clinically in the present series.

In regions where tularemia is prevalent, the disease should be considered when suggested tuberculosis cannot be proved. Agglutination tests for tularemia should be made also in all febrile conditions of the chest which are atypical, especially when the pulse rate is slow and the leukocyte count low with reference to the fever.

SUMMARY AND CONCLUSIONS

The American literature dealing with pleuropulmonary tularemia is reviewed. The clinical data in a series of 95 unselected cases of tularemia are presented and the pleuropulmonary manifestations occurring in this group classified and analyzed. Pneumonia was found in 20 cases, pleural effusion in 13 and bronchitis in 19.

The occurrence of pleuropulmonary changes, especially of pneumonia and pleural effusion, is sufficiently frequent to render them significant clinical manifestations of the disease. Furthermore, in some localities pleuropulmonary tularemia is sufficiently frequent to be considered in the differential diagnosis of all thoracic conditions of obscure causation.

CHANGES IN THE CONTENT OF CARBON DIOXIDE IN VENOUS BLOOD DURING REBREATHING EXPERIMENTS

COMPARISON OF CHANGE IN PERSONS WITH A NORMAL HEART
AND IN PATIENTS WITH CARDIAC DISEASE

HARRY LANDT, M D
AND
JULIEN E BENJAMIN, M D
CINCINNATI

In a previous paper it was shown that persons with a normal heart and patients with cardiac disease behaved differently when subjected to rebreathing experiments¹ When the oxygen in the system reached a concentration ranging between 16 and 13 per cent, the subject began to use less of the gas in the chamber than in the period immediately preceding Subsequently his use of the gas progressively increased The patient with cardiac disease, on the other hand, required increasing amounts of gas, varying according to the severity of his disability The various compensatory mechanisms² invoked during rebreathing experiments have been considered and evaluated (hyperventilation, increased lung volume, increased number of circulating red cells and increased cardiac output) Of these cardiac output is considered of paramount importance This mechanism is known to manifest itself at an oxygen concentration of approximately 14 per cent in normal subjects This compensation is assumed to occur to a lesser degree in those persons whose hearts are incompetent It is apparent that the common denominator of the four compensatory mechanisms is inherent in the changes of gases both centrally and peripherally In the discussion of results in the prior communication,¹ we were unable to state what attending chemical changes occur in the body during rebreathing experiments The studies to be reported here have demonstrated some changes which do occur in the blood when the cardiorespiratory system is subjected to anoxemia

From the Institute for Medical Research of the Jewish Hospital

1 Landt, H, and Benjamin, J Respiratory Changes Produced in the Cardiac Patient by Rebreathing Experiments as Compared with Those of the Normal Individual, *Am Heart J* **15** 83-88 (Jan) 1938

2 Wiggers, C J Physiology in Health and Disease, Philadelphia, Lea & Febiger, 1934, p 398

METHOD

Fourteen persons of comparable ages (20 to 40 years), 7 persons with a normal heart and 7 patients with organic cardiac lesions (mitral stenosis, 5, aortic insufficiency and mitral stenosis, 2) were subjected to rebreathing experiments with a Roth-Benedict metabolator in which air was substituted for oxygen and carbon dioxide was filtered out by means of soda lime. Peripheral vascular disease was not a factor in these cases.

Minute samples of air and of venous blood were analyzed for oxygen and carbon dioxide content, the Haldane and the Van Slyke-Neil technics being used. The samples of blood were collected from the left antecubital vein, with local anesthesia, with the vessel free from stasis and with an oil seal. Duplicate tests were made on all samples of air. Because of the nature and number of blood samples taken, it was thought advisable to make duplicate tests at selected intervals,

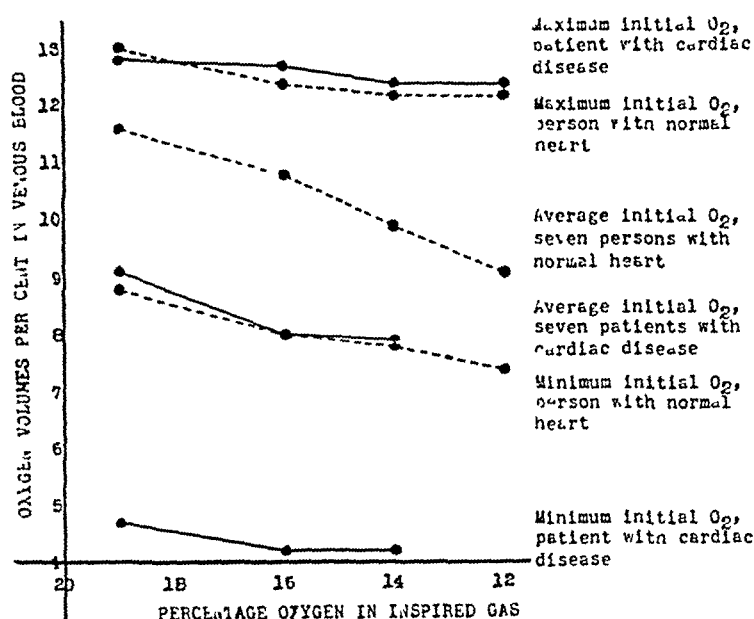


Chart 1—Comparison of changes in the oxygen content of venous blood in persons with a normal heart and in patients with cardiac disease. The points were obtained by graphic interpolation of data.

since it was felt that samples standing longer than three hours tended to show altered gaseous contents. Repeated checks of technic with duplicate and triplicate samples were conducted. Because of the number of samples, the initial samples were taken one minute after the experiment had been in progress.

RESULTS

Both the persons with a normal heart and those with cardiac disease showed a decreasing oxygen content in the venous blood as the rebreathing experiment progressed. The only apparent significant difference noted was in the average initial oxygen levels. From chart 1 it can be readily seen that the average initial oxygen content of the venous blood of the patients with cardiac disease was lower than that of the normal persons. Striking differences were noted when the carbon dioxide con-

tent of the venous blood of patients with cardiac disease was compared with that of normal persons, as the anoxemia progressed Chart 2 shows the curves for patients with cardiac disease and for normal subjects, with the maximum and minimum initial carbon dioxide content in the

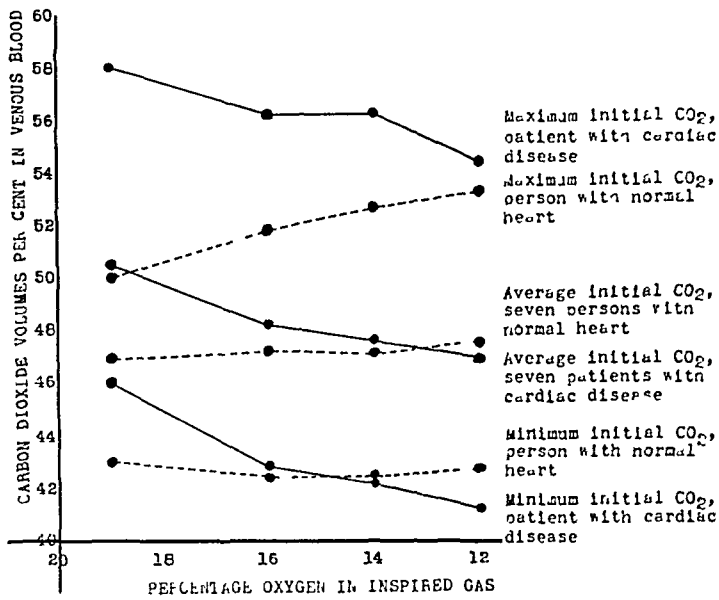


Chart 2—Comparison of changes in the carbon dioxide content in venous blood in persons with a normal heart and in patients with cardiac disease The points were obtained by graphic interpolation of data

Changes in Volumes Per Cent of Oxygen and Carbon Dioxide in Rebreathing Experiments

Summary of Net Results					
Patients with Cardiac Disease			Persons with Normal Hearts		
Patient	Volumes per Cent O ₂	Volumes per Cent CO ₂	Subject	Volumes per Cent O ₂	Volumes per Cent CO ₂
A	-0.6	-4.0	A	-0.8	+0.4
B	-0.8	-7.5	B	-1.5	+2.8
C	-0.9	-5.1	C	-1.6	-0.6
D	-1.1	-3.5	D	-1.6	+0.4
E	-2.5	-2.2	E	-2.4	+0.6
F	-3.6	-6.0	F	-4.6	+3.6
G	-4.3	-6.3	G	-5.4	+0.8
Mean	-1.9	-5.0 ± 2.1	Mean	-2.7	+1.1
H	-1.9	-0.8			

venous blood The patients with cardiac disease showed a progressive decrease in the average carbon dioxide content of the venous blood, as noted in chart 2 Normal subjects showed a slight but progressive increase in the average carbon dioxide content of the venous blood These values will be better understood if one refers to the table This table compares the 7 persons with cardiac disease and the 7 normal subjects with regard to the total variations of oxygen and carbon dioxide

content of the venous blood, measured in volumes per cent. From this comparison it can readily be seen that the average loss of oxygen from the venous blood of the patients with cardiac disease was -1.9 volumes per cent and that of the normal subjects was -2.7 volumes per cent. The average loss of carbon dioxide from the venous blood of the patients with cardiac disease was -5.0 volumes per cent, and the average gain of carbon dioxide in the venous blood of normal subjects was $+1.1$ volumes per cent. All patients with cardiac disease, it will be noted, lost carbon dioxide, the minimum loss being -2.2 volumes per cent and the maximum being -7.5 volumes per cent. All normal persons held or gained carbon dioxide in the venous blood, with the exception of 1, who had a loss of -0.6 volumes per cent. The maximum gain of carbon dioxide in the venous blood of a normal person was $+3.6$ per cent.

COMMENT

Whether the differences in carbon dioxide content noted between the normal subject and the patient with cardiac disease are the result of changes taking place in the peripheral circulation or in the central circulorespiratory unit or in both is a problem for conjecture.

Of particular interest is patient H (table 1). This patient with cardiac disease had a patent ductus arteriosus of a mechanical magnitude severe enough to cause hydraulic failure just six weeks previous to the rebreathing experiment. It will be noted that he lost -1.9 volumes of oxygen and -0.8 volumes per cent of carbon dioxide from his venous blood. These values were comparable to those found in the persons with a normal heart.

It is possible that the relatively greater hyperpnea and relatively slower circulation of the patient with cardiac disease allows greater loss of carbon dioxide in the lungs, the result being modified by conditions at the periphery.

It can be assumed that the loss of carbon dioxide from the blood of the patient with cardiac disease increases the ability of the blood to combine with available oxygen in the lungs.

CONCLUSIONS

Patients with cardiac disease when subjected to rebreathing experiments lose carbon dioxide from the blood stream. Persons with a normal heart either maintain the carbon dioxide content or gain when subjected to like conditions. The loss of carbon dioxide from the blood stream of the patient with cardiac disease allows for a relatively greater oxygen-carrying power in the blood.

DIAGNOSIS OF THE SITE OF ORIGIN OF VENTRICULAR EXTRASYSTOLES IN HUMAN BEINGS

MARIANO R CASTEX, M D

ANTONIO BATTRO, M D

AND

ROBERTO GONZALEZ S, M D

BUENOS AIRES, ARGENTINA

Kraus and Nicolai (1910),¹ owing to the results of experiments with animals, were led to believe that extrasystoles with positive deflection in the right auricle-apex lead were provoked by excitation of a zone of the heart base corresponding to the right ventricle (extrasystole type B = base), that extrasystoles with a negative deflection were due to excitations of the apex (extrasystole type A = apex), and that those with a configuration in "M" were provoked by excitations of the middle portion of the septum (extrasystole type C = central) Kahn (1910)² Rothberger and Winterberg (1913),³ Lewis (1916)⁴ and Padilla (1924)⁵ have proved that the divers forms of extrasystolic complexes are representative not solely of the spot stimulated but also of the ventricle that receives the stimulus According to the results of that research extrasystoles with a negative deflection in lead I start in the left ventricle, and those with a positive deflection in the right one, although it is possible to observe a lack of uniformity in the final results of these experiments, owing to the fact that the excitation of the left ventricle and of the zone adjacent to the apex (Rothberger and Winterberg)

From the Department of Medicine of the School of the University of Buenos Aires

1 Kraus, F, and Nicolai, G Das Elektrokardiogramm des gesunden und kranken Menschen, Leipzig, Veit & Co, 1910

2 Kahn, R H Ueber anomale Herzkammer-elektrogramme, Zentralbl f Physiol **24** 728, 1910

3 Rothberger, C J, and Winterberg, H Studien uber die Bestimmung des Ausgangspunktes ventrikularen Extrasystolen mit Hilfe des Elektrokardiogramms, Arch f d ges Physiol **154** 571, 1913

4 Lewis, T The Spread of the Excitatory Process in the Vertebrate Heart, Phil Tr Roy Soc, London **207** 279, 1916

5 Padilla, T Electrocardiografia Buenos Aires, E Spicelli, 1924, p 418

provokes curves with an inverted deflection as compared with those obtained in other zones of the same ventricle

Marcu (1936),⁶ Loukomski and Guinodman (1937),⁷ bearing in mind the necessity of working with conditions similar to those found in spontaneous extrasystoles, proceeded to stimulate the endocardiac surface of both ventricles in dogs. The results obtained by the authors, under the aforementioned conditions, did not differ from those produced when the stimulus was made on the pericardiac surface. Abramson, Katz, Margolin and Lourie (1937),⁸ working with dogs, cats and monkeys, concluded that it is not possible to localize exactly the starting point of the extrasystoles in either ventricle only by the configuration of the electrocardiographic record.

Some research workers, trying to fix the starting point of extrasystoles in man have endeavored to provoke extrasystoles in patients under special and favorable conditions, as in cases of thoracotomy, with electrical or mechanical stimuli. Studies undertaken by Oppenheimer and Stewart (1926),⁹ Barker, Macleod and Alexander (1930),¹⁰ Marvin and Oughterson (1932),¹¹ Padilla and Cossio¹² (direct stimulus by puncture of the right ventricle, 1932), Vander Vee (1933)¹³ and Lundy and Bacon (1933)¹⁴ proved that extrasystoles with a negative

6 Marcu, I. Experimental Extrasystoles Elicited Through Artificial Stimulation of the Endocardium of the Dog, *Am Heart J* **12** 301, 1936

7 Loukomski, P., and Guinodman, E. Etude expérimentale de l'électrocardiogramme dans l'extrasystole ventriculaire, *Arch mal du cœur* **30** 467, 1937

8 Abramson, D. I., Katz, L. N., Margolin, S., and Lourie, R. Variations in the Electrocardiographic Form of Experimental Ventricular Ectopic Beats Induced in the Monkey and Dog, *Am Heart J* **13** 217, 1937

9 Oppenheimer, B. S., and Stewart, H. J. Dependence of the Form of the Electro-Cardiogram upon the Site of Mechanical Stimulation of the Human Ventricles, *J Clin Investigation* **3** 593, 1927

10 Barker, P. S., Macleod, A. G., and Alexander, J. The Excitatory Process Observed in the Exposed Human Heart, *Am Heart J* **5** 720, 1930

11 Marvin, A. M., and Oughterson, A. W. The Form of Premature Beats Resulting from Direct Stimulation of the Human Ventricles, *Am Heart J* **7** 471, 1932

12 Padilla, T., and Cossio, P. Características electrocardiograficas de la extrasistolia ventricular provocada por puncion cardíaca en el hombre, *Semana med* **39** 1142, 1932

13 Vander Vee, J. B. Premature Beats Produced by the Mechanical Stimulation of the Exposed Human Heart, *Am Heart J* **8** 807, 1933

14 Lundy, C. J., and Bacon, C. M. Premature Left Ventricular Beats from Electrical Stimulation of Exposed Human Heart, *Arch Int Med* **52** 30 (July) 1933

deflection in lead I originated in the left ventricle and those with a positive deflection, in the right one

Extrasystoles in lead II and III give concordant (main initial ventricular deflections in the same direction in all three leads) or discordant curves (main deflections not all in the same direction), according to the level of the ventricular excitation in relation to the long axis of the body (Barkei, Macleod and Alexander) Studies undertaken recently by Lundy, Treiger and Davison (1939)¹⁵ showed a return to the original idea, that a positive or negative polarization of extrasystoles in lead I depends on the starting point of the extrasystoles in relation to the base or apex of the heart The extrasystoles with a starting point at the base have a negative deflection in lead I and those with a starting point at the apex, a positive deflection

It is possible to infer from the aforementioned results that until today there has been no uniformity of criteria in regard to topographic interpretation of extrasystoles

Owing to the intervention of multiple factors, it is not possible to apply the results obtained from experiments in animals to human beings Also, experimental excitation of the pericardiac surface differs widely from spontaneous extrasystoles in human beings For these reasons we have undertaken our research on extrasystoles under normal conditions

We apply the same criterion of investigation to the study of extrasystoles as in the ventricular asynchronism in bundle branch blocks undertaken by Battio, Braun Menendez and Olias¹⁶

ASYNCHRONISM OF VENTRICULAR CONTRACTION UNDER NORMAL AND UNDER PATHOLOGIC CONDITIONS

Under normal conditions both ventricles contract synchronously although a slight physiologic asynchronism can exist owing to a precedence of contraction of one ventricle over the other This physiologic asynchronism, demonstrated in animals by Katz (1933),¹⁷ Eppinger and Rothberger (1910)¹⁸ and Braun Menendez and Solarí (1936),¹⁹ can

15 Lundy, C J , Treiger, Y, and Davison, R Ventricular Extrasystole Induced by Electrical Stimulation of the Exposed Human Heart Rotated Thirty Degrees Counterclockwise on Its Vertical Axis, *Am Heart J* **17** 85, 1939

16 Battio, A , Braun Menendez, E, and Olias, O Asincronismo de la contraccion ventricular en el bloqueo de rama, *Rev argent de cardiol* **3** 325, 1936

17 Katz, L N Asynchronism of the Right and Left Ventricular Contraction and the Independent Variations in Their Duration, *Am J Physiol* **72** 655, 1925

18 Eppinger, H, and Rothberger, C J Ueber die Sukzession der Kontraktion der beiden Herzkammern, insbesondere nach einseitiger Blockierung der Erregungsüberleitung, *Zentralbl f Physiol* **24** 1055, 1910

also be observed in human beings, but it is usually slight, not going over 0.03 to 0.04 second

Under pathologic conditions (bundle branch blocks) asynchronism in ventricular activity is evident not only at the onset of systole but also at the end of it or at the beginning of diastole

Asynchronism at the onset of systole reveals itself in two ways (a) By splitting, dividing or lengthening of the first cardiac sound Two groups of oscillations, one belonging to the isometric systolic phase and the other to the ejection phase, form the component normal parts of the

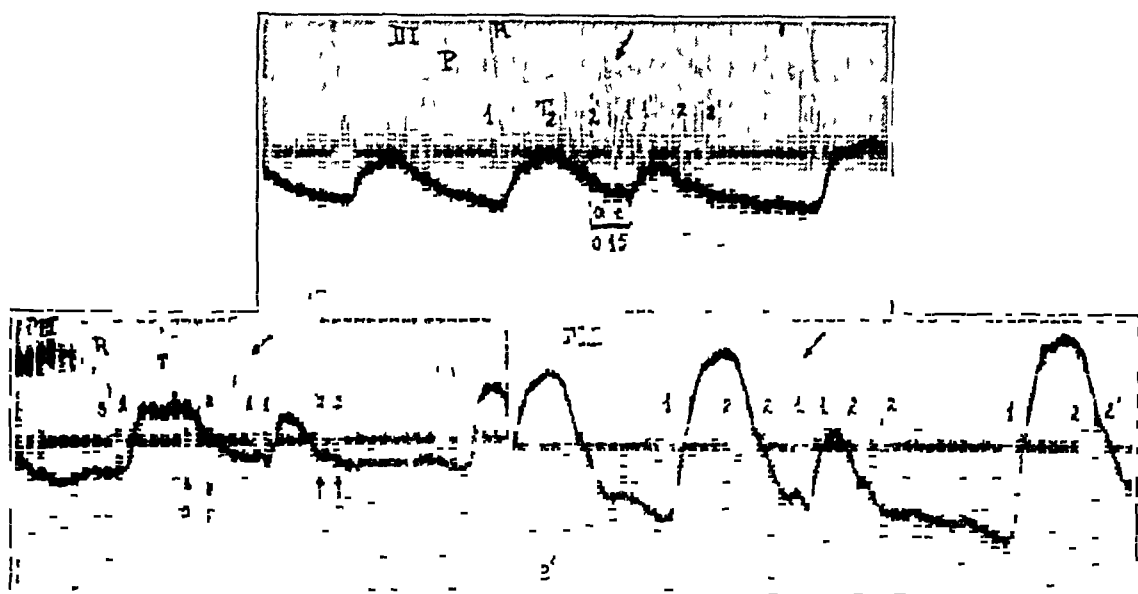


Fig 1—Ventricular asynchronism in a case of extrasystole with a negative initial deflection in lead I and a positive initial deflection in lead III

A, from above downward electrocardiogram in lead I phonocardiogram and central arterial pulse simultaneously recorded Time, 0.04 second The phonocardiogram during ventricular extrasystole shows a clear splitting of the first cardiac sound (1-1'), the final oscillations of which advance more than normally over the ascending limb of the arterial pulse The second sound is also split (2-2')

The first component of the split second sound coincides with the incisura of the arterial pulse (closure of the aortic valves), the second component falls 0.08 second after (closure of the pulmonary valves) QC interval = 0.15 second All these signs indicate that the extrasystole originated in the left ventricle In this particular case the normal beats show also an asynchronism in the closure of the semilunar valves but in an inverted sense as compared with the asynchronism present during the extrasystoles

B, electrocardiogram in lead III and central arterial pulse simultaneously recorded in the same case Two extrasystoles with a positive initial deflection in lead III are to be seen with the same characteristics as in A

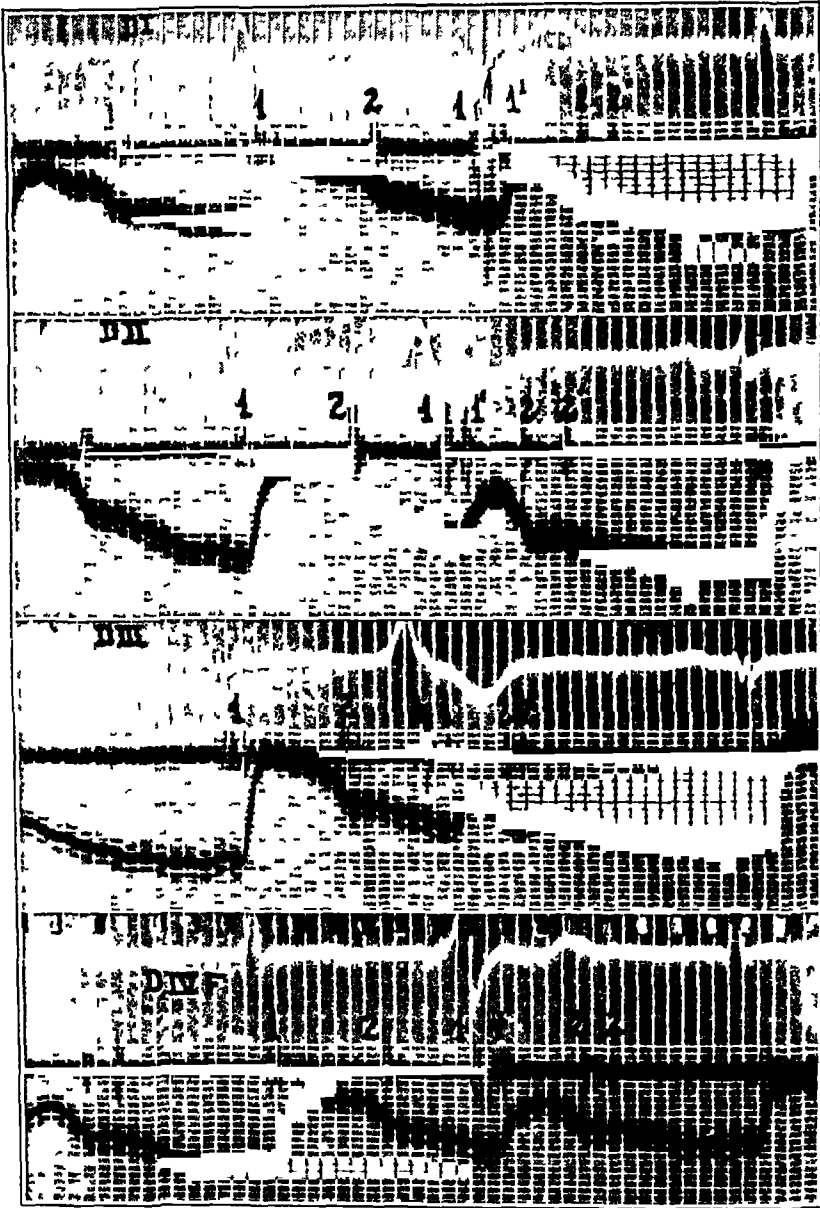


Fig 2—*Extrasystole with a negative initial deflection in lead I*

Electrocardiogram in the four leads simultaneously recorded with phonocardiogram and central arterial pulse. The extrasystole shows splitting of the first (asynchronism of onset of systole) and of the second sound (asynchronism of onset of diastole). The first component of the split second sound coincides with the incisura of the central arterial pulse (closure of the aortic valves) and the second component is registered with delay (closure of the pulmonary valves). QC interval, 0.14 to 0.16 second. These signs indicate that the extrasystole originated in the left ventricle.

first cardiac sound (Caeiro and Orias [1937]²⁰ and Orias and Braun Menendez [1938]²¹) In consequence of anticipated contraction of one ventricle over the other, both component parts remain out of phase and therefore produce the splitting or lengthening of the first cardiac sound

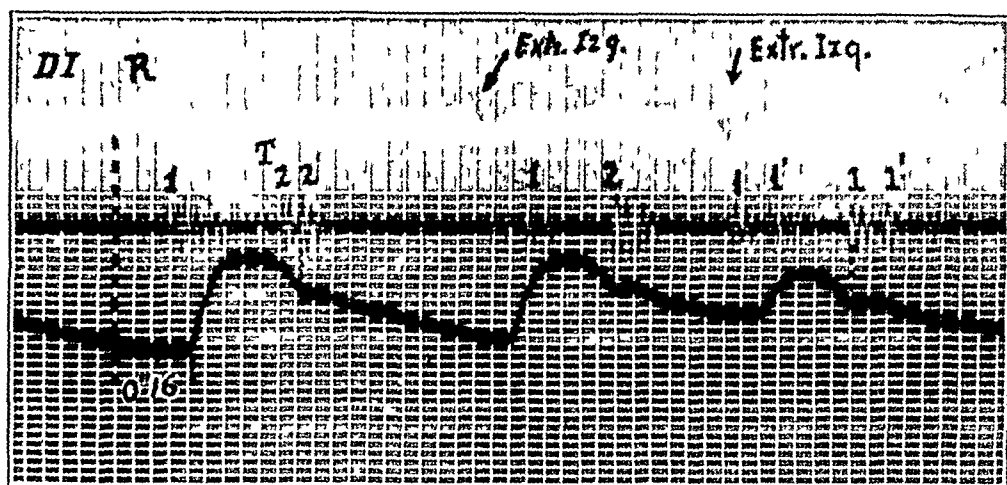


Fig 3—Simultaneous tracings with electrocardiogram in lead I, phonocardiogram and central arterial pulse in a case of left bundle branch block and extrasystole with a negative deflection in lead I

The first electrocardiographic complex shows the basic rhythm of the patient, and the phonocardiogram shows a splitting of the second sound, the first component of which precedes the incisura of the arterial pulse left bundle branch block

The following complexes show two extrasystoles with a negative deflection. The second sound is split, but its first component coincides with the incisura of the arterial pulse, and the second one is registered 0.07 second afterward left ventricular extrasystole

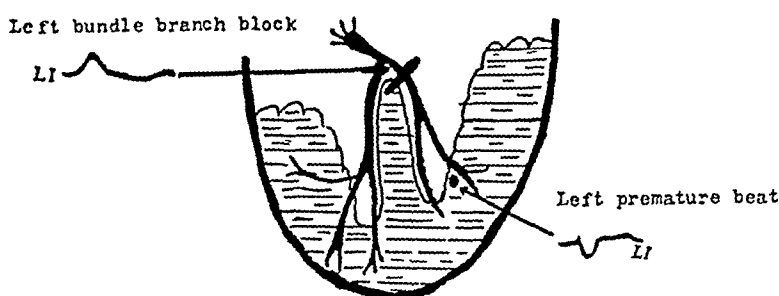


Fig 4—Diagram showing the branch block and the origin of extrasystole (fig 3)

(b) By modifications of the QC time, which is the interval between the onset of the QRS complex in the electrocardiogram and the onset of

20 Caeiro, and Orias, O El fonocardiograma registrado en los distintos focos de auscultacion Sus caracteres y relaciones en el pulso venoso y el electrocardiograma, Rev argent de cardiol 4 71, 1937

21 Orias, O, and Braun Menendez, E Los ruidos cardiacos, Buenos Aires, El Ateneo, 1937

the central arterial pulse, which shows the activity of the left ventricle. The QC interval in normal conditions has a mean value of 0.12 second.

Asynchronism at the end of systole or onset of diastole is shown by the splitting of the second sound. The ventricle that has been the first to contract ends its systolic activity or begins its diastolic period before the opposite ventricle. The closing of the aortic and pulmonary semilunar valves takes place in consequence asynchronously, one after the other.

It is possible to determine which valve is the first to close by the relation of the two components of the split second sound to the incisura of the central arterial pulse or by the oscillations shown on the ascendant branch of the "V" wave (both representing the closure of the aortic semilunar valves).

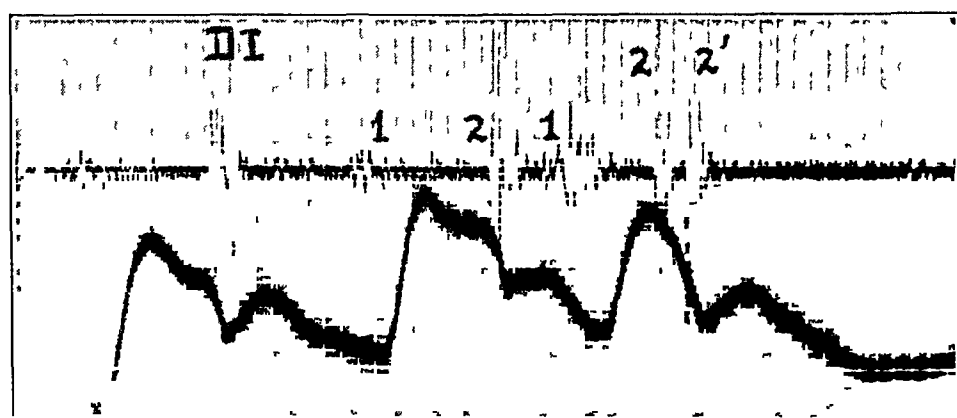


Fig. 5—Ventricular asynchronism in a case of extrasystole with an upward initial deflection in lead I.

The first sound of the extrasystole is larger and of longer duration than those of the normal beats, but it does not advance over the ascending limb of the arterial pulse, as in figures 1 and 2. The second sound is split, its first component precedes by 0.08 second the incisura of the arterial pulse, and its second component coincides with the incisura. QC interval, 0.20 second. There is in this case of extrasystole an asynchronous closure of semilunar valves, the pulmonary valves closing before the aortic, indicating right ventricular extrasystole.

METHOD

In our work we recorded simultaneously the electrocardiogram (in lead I, occasionally in lead III or leads I, II, III and IV F), phonocardiogram and central arterial or venous pulse. For our electrocardiograms and phonocardiograms we have utilized the all-electric Cambridge unit. The mechanical tracings of arterial and venous pulse have been undertaken by means of Frank's capsules with optical methods. The tracings were obtained excluding all parallax.

According to this method, the first cardiac sound, under normal conditions, lasts from 0.06 to 0.08 second, and the second cardiac sound from 0.04 to 0.08 second. The onset of the second sound coincides with the bottom of the incisura of the central arterial pulse or precedes it by 0.01 to 0.03 second.

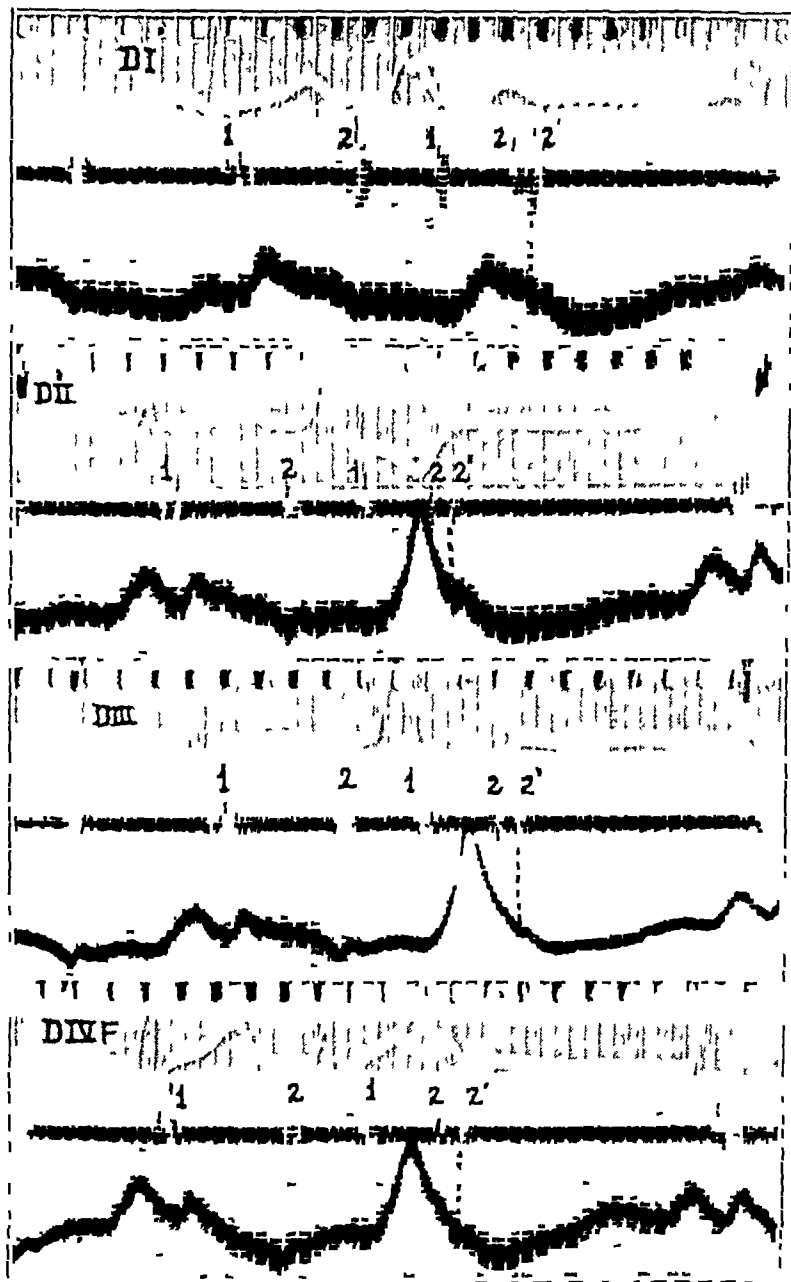


Fig 6—Extrasystole with an upward initial deflection in lead I

Electrocardiogram in four leads, simultaneously with phonocardiogram and venous pulse (arterialized venous pulse). The second sound of the extrasystole is split, and its first component precedes the notch which in the venous pulse represents the closure of aortic semilunar valves. The second component coincides with the notch. There is an asynchronous closure of semilunar valves, the pulmonary valves closing before the aortic. The extrasystole arises in the right ventricle.

RESULTS

Applying the aforementioned procedure we have studied 23 cases 13 with premature beats with an initial upward deflection and 10 with an initial downward deflection in lead I. In nearly all our observations we have simultaneously registered either phonocardiogram central arterial

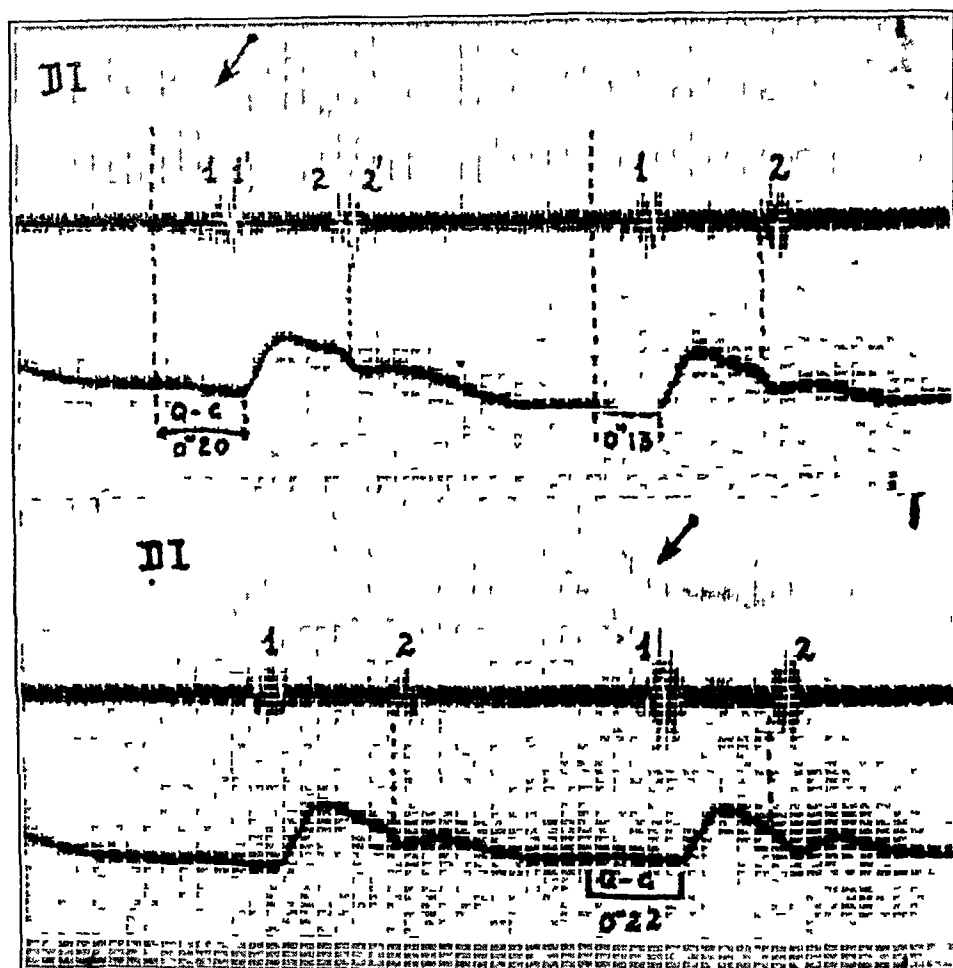


Fig 7—Ventricular asynchronism during extrasystole with a positive initial deflection in lead I

(The lower record is a continuation of the upper one) The first extrasystole with its split second sound shows clearly an asynchronous closure of the semilunar valves with characteristics of the former case (fig 6). In the second extrasystole the second sound shows no splitting but begins 0.07 second before the incisura of the arterial pulse, indicating a similar grade of asynchronism. The QC interval is 0.20 and 0.22 second in each case. Both extrasystoles originate in the right ventricle.

pulse and electrocardiogram or phonocardiogram, venous pulse and electrocardiogram

1 *Ventricular Extrasystoles with Downward Deflection in Lead I*—In 10 cases we have ascertained a splitting, dividing or lengthening of the first cardiac sound, a lengthening of the QC interval and a splitting of the second sound

A The length of the first sound exceeds 0.08 second (normally 0.06 to 0.08), and the final oscillations climb longer than normal on the ascendant branch of the central arterial pulse (figs. 1 and 2)

B The QC interval, the time between the onset of the ventricular complex of the electrocardiogram and the rising of the central arterial pulse, measured in 46 extrasystoles of these 10 cases, had a minimum of 0.11 a maximum of 0.22 and an average of 0.17 second

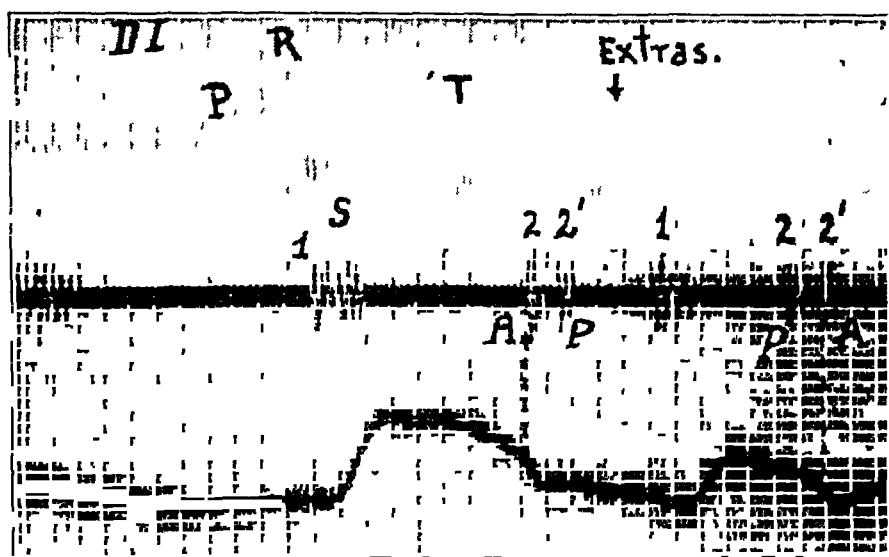


Fig. 8—*Ventricular extrasystole with positive deflection in lead I*

The first systole, which indicates the basic rhythm of the patient, is of the type "deep S wave in lead I" and shows an asynchronism, with the closing of the aorta (*A*) before that of the pulmonary artery (*P*). The asynchronism is inverted in the extrasystole, the pulmonary closing preceding that of the aorta. The QC interval is 0.20 second right ventricular extrasystole

C The two components of the split second sound had in these cases the following time relations. The first component coincided with the bottom of the incisura of the arterial pulse or preceded it by 0.01 to 0.03 second and coincided also with the notch of the ascending limb of the "V" wave of the venous pulse, the second component of the split sound followed the first by an interval of 0.06 to 0.08 second

When the ventricular extrasystole of downward deflection in lead I shows itself in a case of left bundle branch block (fig. 3), the splitting of the second sound of the extrasystolic complex in regard to the incisura

of the central arterial pulse takes place in an inverted sense to the basic contractions. In the left bundle branch block, the first component part of the split second sound precedes the incisura of the arterial pulse and the second component part coincides with the same. In the extrasystoles, the first component part coincides with the incisura and the second component part is registered afterward.

2 Ventricular Extrasystoles with Upward Deflection in Lead I— Of this type we have observed 13 cases. We have proved that a splitting or lengthening of the first sound takes place. The splitting or lengthening is not as clear as in the preceding cases, but it has a peculiarity in

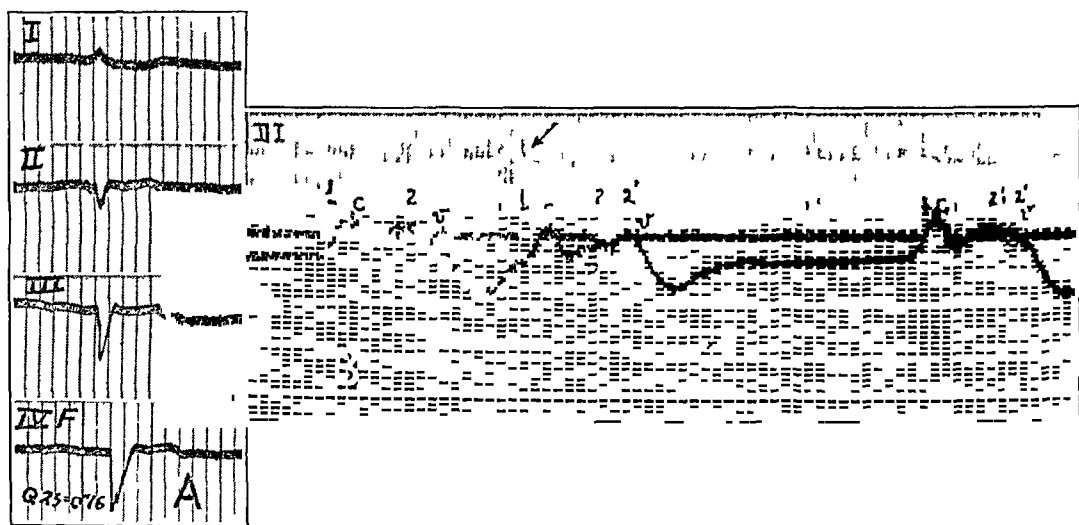


Fig 9—Left bundle branch block and extrasystole with positive deflection in lead I

A, electrocardiogram in four leads. *B*, simultaneous electrocardiogram, phonocardiogram and venous pulse of the same patient. The asynchronism at the end of systole (splitting of the second sound) is in the same direction in block contraction as during extrasystole but is more evident in the latter. The first component part precedes the oscillations of the ascending branch of the "V" wave in the phlebogram of right ventricular extrasystole.

that the oscillations of the first part do not climb so much as normal on the ascending branch of the central arterial pulse.

The Q-C interval, measured in 77 extrasystoles of the 13 cases, gave a minimum of 0.16, a maximum of 0.28 and an average of 0.22 second.

The second sound showed a splitting also, but with the peculiarity that the first component part preceded the incisura of the central arterial pulse and the oscillations of the ascending branch of the "V" wave of the venous pulse by 0.06 to 0.12 second. The second component part coin-

cided with the incisura and with the oscillations of the ascending branch of the venous pulse (figs 5, 6, 7 and 8)

When extrasystoles with an upward deflection in lead I appear in a case of left bundle branch block, as in figure 9, the splitting of the second sound is in the same relation to the arterial or venous pulse as in the block

When in the same tracings ventricular extrasystoles take place with an upward or downward deflection in lead I, the splitting of the second

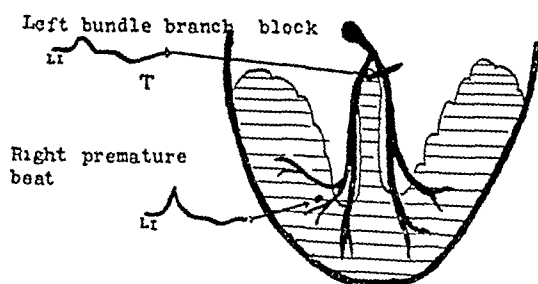


Fig 10—Diagram showing the branch block and the origin of extrasystole (same case as that shown in figure 3)

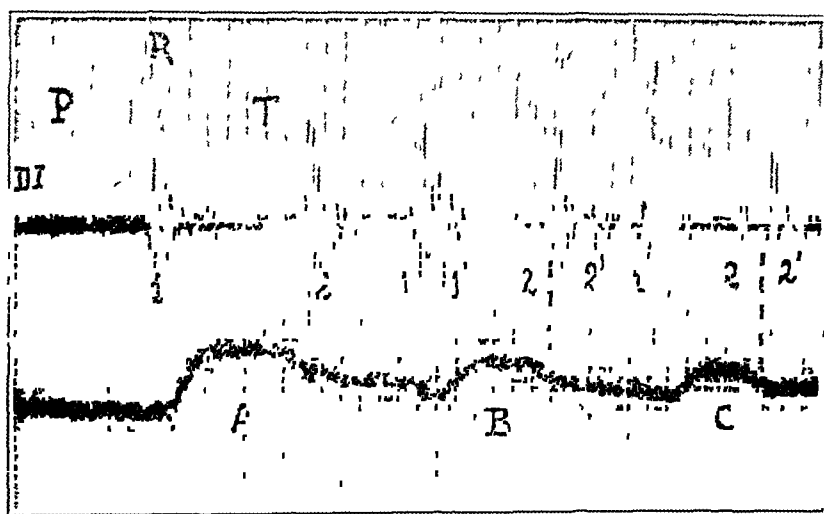


Fig 11—Extrasystoles with negative and positive initial deflection in lead I

A, normal beat B and C, extrasystoles The second sound is split in both extrasystoles In the extrasystole with negative initial deflection the first component of the split second sound coincides with the incisura of arterial pulse, in the extrasystole with positive initial deflection the first component of the split second sound precedes the incisura The first extrasystole originates in the left ventricle, the second in the right ventricle

sound, in relation to the central arterial pulse, shows the characteristics we have assigned it but in an inverted sense in one or another extrasystole (fig 9)

COMMENT

When extrasystole occurs with a negative deflection in lead I, we have been able to prove (1) splitting, lengthening or dividing of the first cardiac sound, with the final oscillation covering over the ascending branch of the central arterial pulse, (2) lengthening of the QC interval (0.17 second, average), and (3) splitting of the second cardiac sound, of which the first component part coincides with the incisura of the central arterial pulse and with the oscillations of the ascending branch of the "V" wave of the venous pulse, and the second component part is registered 0.06 to 0.08 second after the onset of the first

When extrasystole occurs with a positive deflection in lead I, we have also determined (1) splitting, lengthening or dividing of the first sound, (2) lengthening of the QC interval (0.22 second, therefore more than formerly), and (3) splitting of the second sound with the first component part preceding in 0.06 to 0.12 second the incisura of the central arterial pulse and the second component part coinciding with the incisura of the central arterial pulse

All these manifestations show, in our opinion, the ventricular asynchronism which takes place during extrasystoles of the ventricles. Fundamentally the extrasystoles are a consequence of a premature excitation taking place in the subendocardial surface, among the fibers (Purkinje) of the conductive system. The stimulating wave that produces a premature contraction of a ventricle is transmitted by the muscle wall to the opposite one. Owing to the delay with which this wave is transmitted by the cardiac muscle, the other ventricle receives the stimulus in a deferred manner, and therefore the manifestation of its contractile activity shows delay in relation to that of the ventricle first activated. Our results prove logically this ventricular asynchronism, which makes itself evident not only at the onset of systole but also at the end of systole or the onset of diastole.

The splitting, lengthening or dividing of the first cardiac sound is the manifestation of the asynchronism that takes place at the beginning of systole, and the splitting of the second cardiac sound is the result of the asynchronism at the end of systole, in accordance with the reasons we have given when treating asynchronism associated with pathologic conditions.

When extrasystole occurs with a negative deflection in lead I, we have observed that the final oscillation of the first sound is longer than normal and covers over the ascending branch of the arterial pulse, a phenomenon that does not occur with extrasystoles of a positive deflection, in which the final oscillation of the first sound coincides with the onset of the pulse.

Our interpretation of these facts is that when extrasystole occurs with a negative deflection in lead I, the first oscillation of the first sound originates in the left ventricle and the final oscillation, prolonging itself over the ascending branch of the arterial pulse, originates in the right ventricle.

We deduce that there is an asynchronism of the onset of systole, due to anticipation of the activity of the left ventricle over that of the right one.

When extrasystole occurs with a positive deflection, the initial oscillation of the first sound corresponds to the contraction of the right ventricle, and the final oscillation, which coincides with the beginning of the rising of the arterial pulse, corresponds to the contraction of the left ventricle. The right ventricle precedes the left one in contraction.

In regard to the splitting of the second sound, we have proved that when extrasystole occurs with a negative deflection in lead I, the first component part of the split second sound coincides with the incisura of the central arterial pulse and, therefore, corresponds with the closing

Interval Between the Onset of QRS and the Onset of the Arterial Pulse (QC Interval)

	Number of Cases	Number of Extra systoles	Time, Seconds		
			Minimum	Maximum	Average
Normal contractions	76		0 08	0 16	0 12
Extrasystoles with negative deflection in lead I	10	46	0 11	0 22	0 17
Extrasystoles with positive deflection in lead I	13	77	0 16	0 28	0 22

of the aortic valves. The second component part, which is registered with delay, is the result of the closing of the pulmonary valve. This fact shows that the closing of aortic semilunar valves precedes that of the pulmonary semilunar valves.

When extrasystole occurs with a positive deflection in lead I, the contrary takes place, which means that the closing of the pulmonary semilunar valves precedes that of the aortic ones.

The ventricle the semilunar valves of which close first must be logically the one that has contracted first and therefore has been the one to receive the excitation first. When extrasystole occurs with a negative deflection in lead I, the left ventricle anticipates its contraction over the right one, in opposition to what happens when extrasystole occurs with a positive deflection in lead I.

Finally, the QC interval (usually lengthened during ventricular extrasystole, owing to the slowness of the propagation of the pulse wave of extrasystolic contraction) is more prolonged during an extrasystole with a positive deflection in lead I than during one with a negative deflection in lead I (table). In our opinion, this fact is logically a consequence

of ventricular asynchronism at the onset of contraction. The QC time should be longer when the left ventricle receives its excitation wave with delay, and therefore its contractile activity is also deferred, as the wave of the arterial pulse represents the activity of the left ventricle. This fact we proved during extrasystole with a positive deflection in lead I, when the QC time is longer than during extrasystole with a negative deflection. This means that the left ventricle contracts after the right one.

If extrasystole appears in a case of bundle branch block, the ventricular asynchronism is inverted when the extrasystole starts in the ventricle of which the branch is blocked but not when the extrasystole starts in the other ventricle. We therefore deduce that in case of a left bundle branch block (figs 5 and 11) in which the right ventricle precedes the left one in its activity, the extrasystoles of a negative deflection show the precedence of the left ventricle, and those of a positive deflection, the precedence of the right ventricle. This fact tends to confirm our aforementioned interpretation of the origin of extrasystoles according to deflection in lead I.

SUMMARY AND CONCLUSIONS

Electrocardiograms and phonocardiograms registered simultaneously with tracings of central arterial or venous pulse allow us to prove asynchronism of ventricular contraction and also to determine which of the ventricles contracts first.

In this manner we have studied 23 cases of spontaneous extrasystoles in human beings (10 showing negative deflection and 13, positive deflection in lead I), and we have been able to determine to which ventricle corresponds the priority in contraction.

When extrasystole occurs with a negative deflection in lead I the data obtained show that the left ventricle contracts before the right one.

When extrasystole occurs with a positive deflection in lead I, the manifestations of asynchronism show priority of contraction in the right ventricle over that in the left one.

By the facts stated, we consider ourselves justified in concluding that premature beats with negative deflections in lead I originate in the left ventricle and those with positive deflections in lead I, in the right ventricle.

TUMORS OF THE HEART

REPORT OF FOUR CASES AND REVIEW OF LITERATURE

JAMES R. LISA, M.D.

LOUIS HIRSCHHORN, M.D.

AND

CRAWFORD A. HART, M.D.

NEW YORK

During the summer of 1937 there came under observation at the New York City Hospital, Welfare Island, a case of intractable cardiac dysfunction. Certain features presented by the patient suggested the presence of a malignant tumor of the heart. We were able to confirm the diagnosis later by autopsy. Search of the records in the pathologic laboratory revealed 3 other cases of cardiac disease due to neoplasm. These 4 cases form the basis of this report.

REPORT OF CASES

CASE 1—*Lymphosarcoma of upper retroperitoneal and mediastinal lymph nodes, with metastases to heart, pleura, lungs, diaphragm, pancreas, thyroid and kidneys*

A white married woman aged 17, seven months pregnant, was admitted to the obstetric division, service of Dr. K. Johnson, on May 11, 1937. The family history was essentially irrelevant. She had been born with forceps delivery and breast fed for three or four months. Until the age of 5 years she was always well, but during the next two years, when in contact with other children, she contracted whooping cough, measles, German measles and scarlet fever. Since that time she had mild chest colds every fall and sore throat once or twice every winter. When she was 15 years of age there occurred a severe attack of dyspnea and "lump in the throat", the cause of this condition could not be determined from available data. In the summer of 1936, one year before admission, however, she was able to carry on strenuous athletics, frequently swimming across the East river.

During the first few months of pregnancy there was the usual morning sickness. Since March there had been vomiting, dizziness, fainting and edema of the legs.

Examination—The patient was a nervous young woman, in the seventh month of pregnancy. She was orthopneic and cyanotic, in a state of evident cardiac failure. The vessels of the neck pulsated. The heart was enlarged to the anterior axillary

From the Pathological Laboratory, Second Medical Division, service of Dr. W. L. Whittemore, and the Obstetrical Division, service of Dr. K. Johnson, New York City Hospital, Welfare Island, Department of Hospitals.

line The apical sounds were muffled and of poor quality, and the rate was 140 The blood pressure was 125 systolic and 65 diastolic A to and fro murmur was present over the precordium Fluid at the base of the right lung extended to the scapular angle The feet and finger nails were slightly cyanotic The liver, enlarged to the umbilicus, was tender and did not pulsate A blood count revealed a hemoglobin value of 68 per cent, 3,450,000 erythrocytes and a normal number of white cells The Wassermann reaction of the blood was negative The urine contained albumin, 1 plus, and sugar, 1 plus The temperature was normal There was no evidence of venereal infection

Course—For the next four days the patient remained acutely ill, dyspneic and cyanotic The pulse rate was rapid, 120 to 140, and there was a gallop rhythm She had low blood pressure, 100 systolic and 60 diastolic When oxygen and digitalis were administered there was considerable improvement The pulse became stronger, the rate dropping to 108 The heart sounds improved in quality The liver remained large and tender The edema of the legs disappeared On May 21, ten days after admission, she was much better Dyspnea and cyanosis were diminished and the gallop rhythm and rales had disappeared The pulse rate remained rapid, and the heart sounds, although somewhat better, were not of good quality

On May 27 labor began A few drops of ether, given by the open drop method, caused such intense cyanosis that the administration of the drug was discontinued and the patient was allowed to deliver the child spontaneously The total time of labor was five and a half hours At the end of labor her condition was only fair The pulse had a rate of 140 and was regular and without deficit The following morning cyanosis was intense, orthopnea had increased but pulmonary rales were absent The liver was still enlarged to the umbilicus There was slight edema of the ankles The patient was transferred to the Second Medical Division

The course until her death, on July 4, was characterized by intense dyspnea, cyanosis, unrelieved by any procedure, marked tachycardia and rapid accumulation of fluid in the chest and pericardium It was noteworthy that at no time after delivery was there any improvement in the cardiac status and that there were progressive emaciation and cachexia The liver remained large and tender Edema of the ankles and sacrum was noted but was never marked Cardiac pain occurred only once On June 3 the left arm was swollen and soon became cold, blue and hypersensitive The axillary, subclavian and superficial veins of the neck were palpable and cordlike This swelling slowly subsided but never completely disappeared

Frequent taps of pleural and pericardial sacs were done, sometimes producing marked relief There were five taps of the right portion of the chest, one of the left and six of the pericardium The right part of the chest yielded as much as 1 liter of fluid, the first removed was yellow-green, and that removed after the following taps was serosanguineous The pericardial fluid was always bloody and usually the quantity was between 400 and 800 cc Examinations for bacteria and malignant cells gave consistently negative results

The blood pressure remained low and fairly constant, the systolic and diastolic being 110 and 70, 95 and 80, 130 and 80, and 110 and 60 mm of mercury respectively

Up to the time of delivery the temperature remained normal with a range of 97 to 99 F On the three subsequent days it reached 100 F, remaining at that

level until the ninth day, then it rose rapidly to 102 and 103 F, fell to normal for one day and then fluctuated for ten days from 99 to 103 F. The last two weeks it varied from 98 to 101 F. The pulse always showed tachycardia, the rate ranging from 100 to 150. The rate of respirations was from 36 to 50.

The value for hemoglobin remained practically constant, being 68 or 64 per cent. The urine always had a trace of albumin, a few clumps of pus cells, red blood cells and sometimes sugar.



Fig 1 (case 1) —Metastatic lymphosarcoma diffusely involving the base of the heart and the auricles and extending down to the apex

The results of electrocardiographic studies were as follows. On May 18 there was normal sinus rhythm. The auriculoventricular conduction time was normal, the rate was 115. The P waves in lead III were inverted, and there was right deviation of the electrical axis. On May 24 the sinus rhythm and the auriculoventricular conduction time were again normal. There was simple tachycardia.

All T waves were abnormal, and there was right axis deviation. On June 1 there was normal sinus rhythm. The rate was 136. The T waves in lead I showed low voltage. The T waves were diphasic in leads II and III. On June 4 the sinus rhythm was again normal and the rate again 136. There was normal auriculoven-

tricular conduction time The T waves in lead I were flattened and those in leads II and III, inverted The QRS complete was slurred, and there was low voltage in all leads The most prominent features revealed by roentgenologic studies were the tremendous enlargement of the cardiac shadow, which persisted in all examinations, the widened mediastinum and the widened pulmonary vessels The contour at first suggested rheumatic heart disease but was not characteristic Later it was similar to that of pericardial effusion

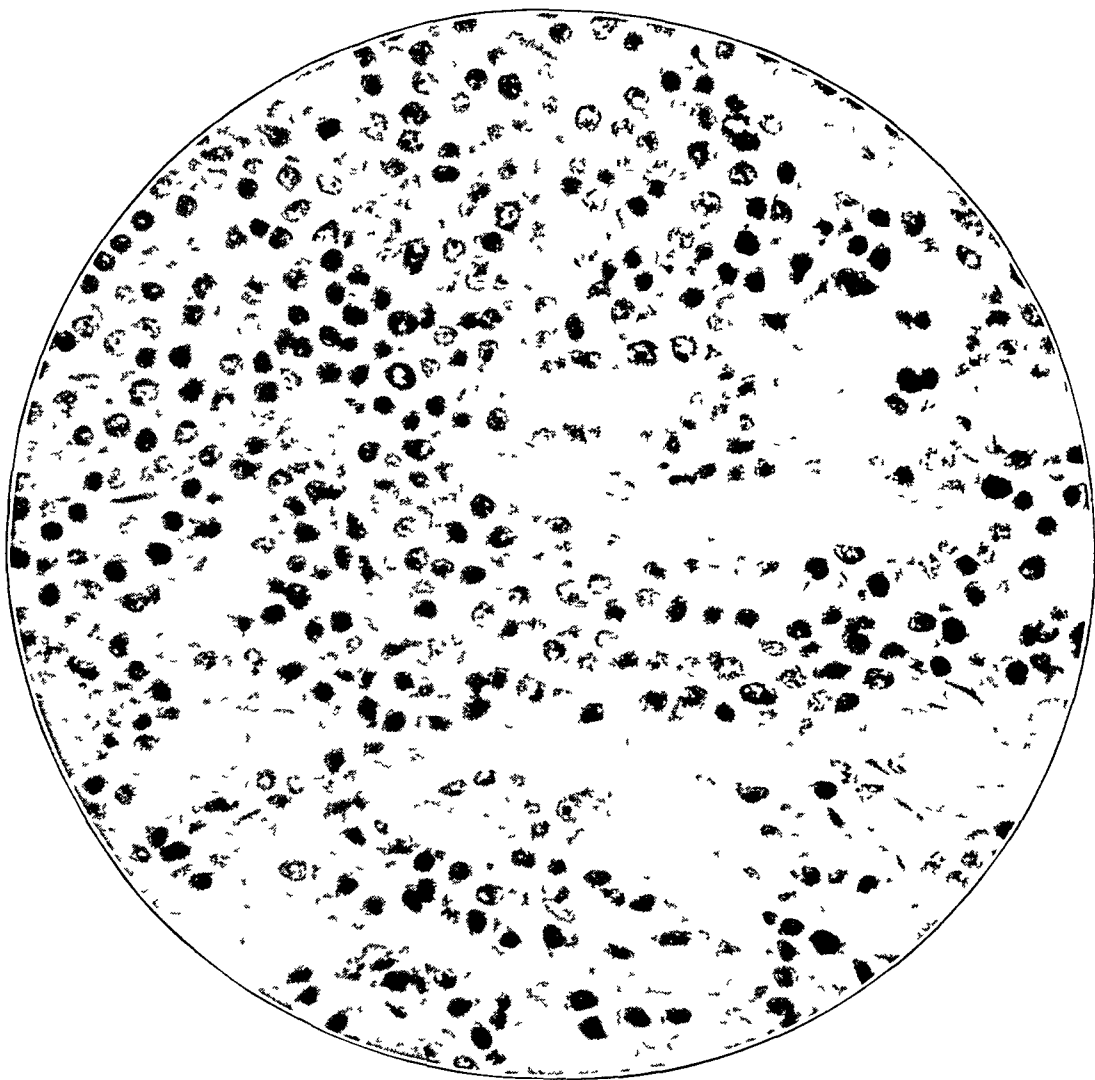


Fig 2 (case 1) —Section through the auricles showing replacement by lymphosarcomatous tissue and marked degenerative myocardial changes

Necropsy—Postmortem examination was performed five hours after death The heart weighed 650 Gm (fig 1) The pericardial sac was distended by more than 1 liter of serosanguineous fluid The pericardium was studded with whitish nodules Large white masses of tumor tissue had practically destroyed the myocardium The auricles and the interauricular wall appeared completely replaced, and in the ventricles were large masses, the only easily identifiable muscle being at the apex and in the subendocardial layers of the ventricles Tumor tissue projected

into the coronary sinus, but the endothelium was preserved and thrombosis was absent. All the large veins were compressed. The superior vena cava and its tributaries were occluded by nonmalignant thrombus.

The histologic examination showed lymphosarcoma (fig 2).

CASE 2—Carcinoma of left kidney, carcinomatous thrombosis of left renal vein, metastases to retroperitoneal, thoracic and lower cervical lymph nodes, heart and right femur.

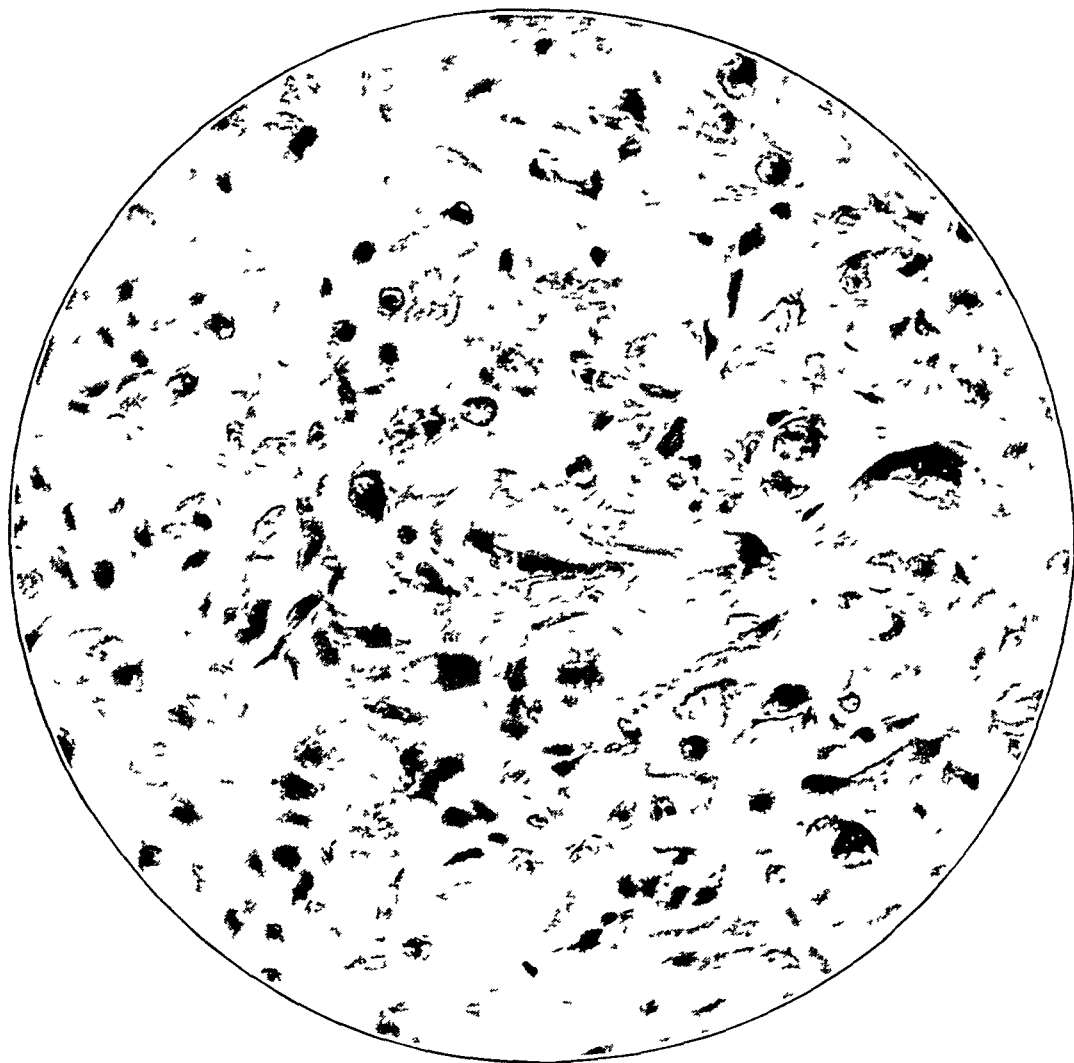


Fig 3 (case 2)—Anaplastic carcinoma arising from a primary carcinoma of the kidney.

A white man aged 74 was admitted to the First Medical Division, service of Dr D S Likely, on Nov 15, 1937. The history was difficult to obtain because the patient spoke little English. For two or three months he had noticed a somewhat painful mass on the right leg and for about one month had had precordial pain and an unproductive cough.

Examination—The patient appeared chronically ill but was cooperative and cheerful. Cervical, left axillary and inguinal nodes were enlarged and nontender. A hard, immovable, slightly tender mass, about the size of an apple, was present

above the mesial condyle of the right femur. The heart was not enlarged. The sounds were of poor quality. The rhythm was regular. The pulse rate was 90 and the blood pressure 80 systolic and 50 diastolic. A mass deep in the left upper quadrant could be felt but not definitely outlined.

Course—On the following morning the blood pressure had risen to 140 systolic and 70 diastolic and 115 systolic and 65 diastolic. The abdomen was held somewhat rigidly, but the mass could be palpated, the lower pole being felt at the level of the umbilicus. The blood count was as follows: hemoglobin 62 per cent, red blood cells 4,110,000 and white cells 15,950. The urine gave a 2 plus reaction for sugar and contained a few red and white blood cells. The nonprotein nitrogen value of the blood was 129 mg, and the sugar content 121 mg, per hundred cubic centimeters. On the afternoon of November 18, three days after the patient's admission, the left foot and then the fingers became cyanotic. He rapidly became weaker, and death occurred in thirty minutes. The temperature was 98 to 99 F, and the pulse rate was always rapid, from 90 to 110.

Necropsy—Postmortem examination was performed twenty hours after death. The heart weighed 450 Gm. There were numerous tumor nodules in the interventricular wall, the left ventricle and the apex of the right ventricle. The largest and most numerous were in the interventricular wall. The proximal portion of the anterior descending artery had marked sclerosis without narrowing, the other arteries were moderately atheromatous.

Histologic examination showed metastatic carcinoma (fig. 3).

CASE 3—Carcinoma of left main bronchus, lymphatic permeation of lungs, metastases to tracheobronchial and upper abdominal lymph nodes, pericardium, liver, kidneys, adrenal glands and ribs, carcinomatous emboli of myocardial branches of coronary arteries, with acute mihiary infarctions of heart

The patient, an acutely ill, emaciated white woman was admitted to the First Medical Division, service of Dr. W. I. Reardon, on Oct. 13, 1938. She complained of racking cough, pain in the left portion of the chest, knees and back, expectoration of large amounts of thick white sputum, night sweats and loss of weight, all the symptoms being of five weeks' duration. There were other symptoms of less prominence: breathlessness on walking up one flight of stairs, anorexia, constipation and frequency of urination associated with burning.

The family history as well as the previous personal history was entirely normal. The pains in the knees and back were severe enough to prevent moving about or walking freely. The loss in weight was 15 pounds (6.8 Kg.).

Examination—The pertinent physical findings were as follows. There was diminished expansion of both sides of the chest. The supraclavicular and infraclavicular spaces of both sides were depressed. There was dullness of the left portion of the chest anteriorly and diminished resonance of both upper portions posteriorly. Diffuse rhonchi were observed bilaterally. Dyspnea was present. There was fever, the temperature being 102.2 F. Marked tachycardia (pulse rate, 114) was observed, but there were no thrills or murmurs and no pulse deficit. The knees were painful, but no physical changes could be demonstrated. The spine was not tender on palpation.

The Wassermann reaction of the blood was negative. The urine had a specific gravity of 1.025 and contained albumin (1 plus), occasional granular casts and

a few white blood cells Examination of the blood revealed a hemoglobin content of 10 Gm per hundred cubic centimeters, red cells 4,800,000 and white cells 24,000 Tests of the sputum for tubercle bacilli gave negative results

Roentgen examination showed the entire left pulmonary field to be obscured by a diffuse shadow The heart and mediastinum were pulled to the same side, and the left main bronchus was obstructed or kinked

Bronchoscopy was performed on October 20 Although not in good general condition, the patient stood the procedure well The carina was thick and edematous

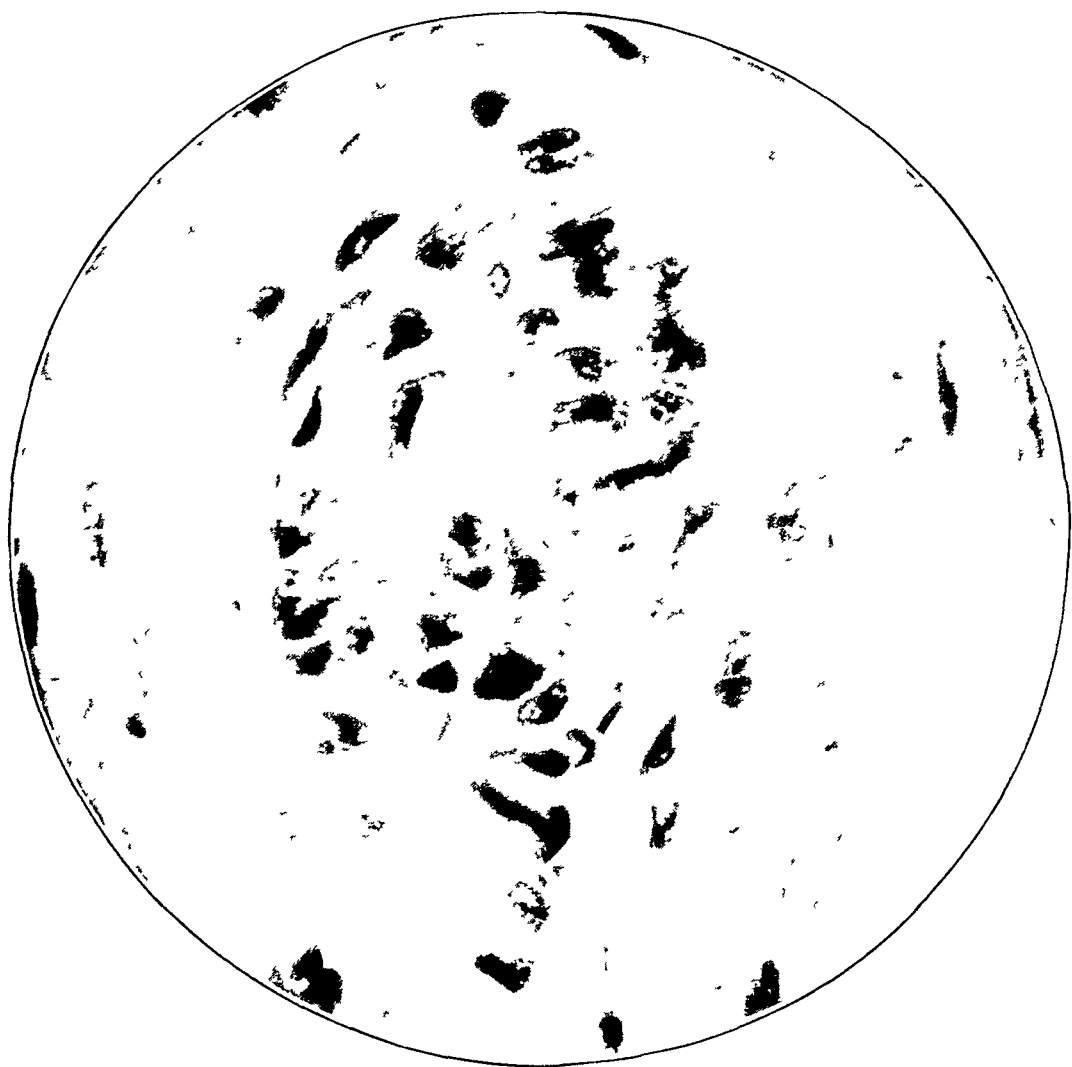


Fig 4 (case 3)—Carcinomatous emboli of the myocardial branches of the coronary arteries The original tumor was a bronchogenic carcinoma of the lung

The entire left main bronchus was inflamed, swollen and ulcerated, and the mucosa bled easily There was marked stenosis but no obstructing mass Neither excess secretion nor odor was observed Biopsy showed squamous cell carcinoma

Course—From the time of her admission, the condition of the patient, although poor, changed but little Incontinence of urine and feces and severe sweats were present occasionally The material expectorated was only moderately abundant and was blood streaked only after bronchoscopy On the evening of October 23,

five days after admission, she suddenly became much worse. The respirations became labored and the pulse faint and rapid, perspiration about the head and face became severe. The course was rapidly progressive, and death ensued within twenty-four hours.

Throughout the entire period of hospitalization, the temperature fluctuated between 100 and 102 F. The pulse rate was consistently rapid (100 to 130), the last twenty-four hours the beat being too rapid and weak to count accurately. The respiratory rate was 32 to 48.

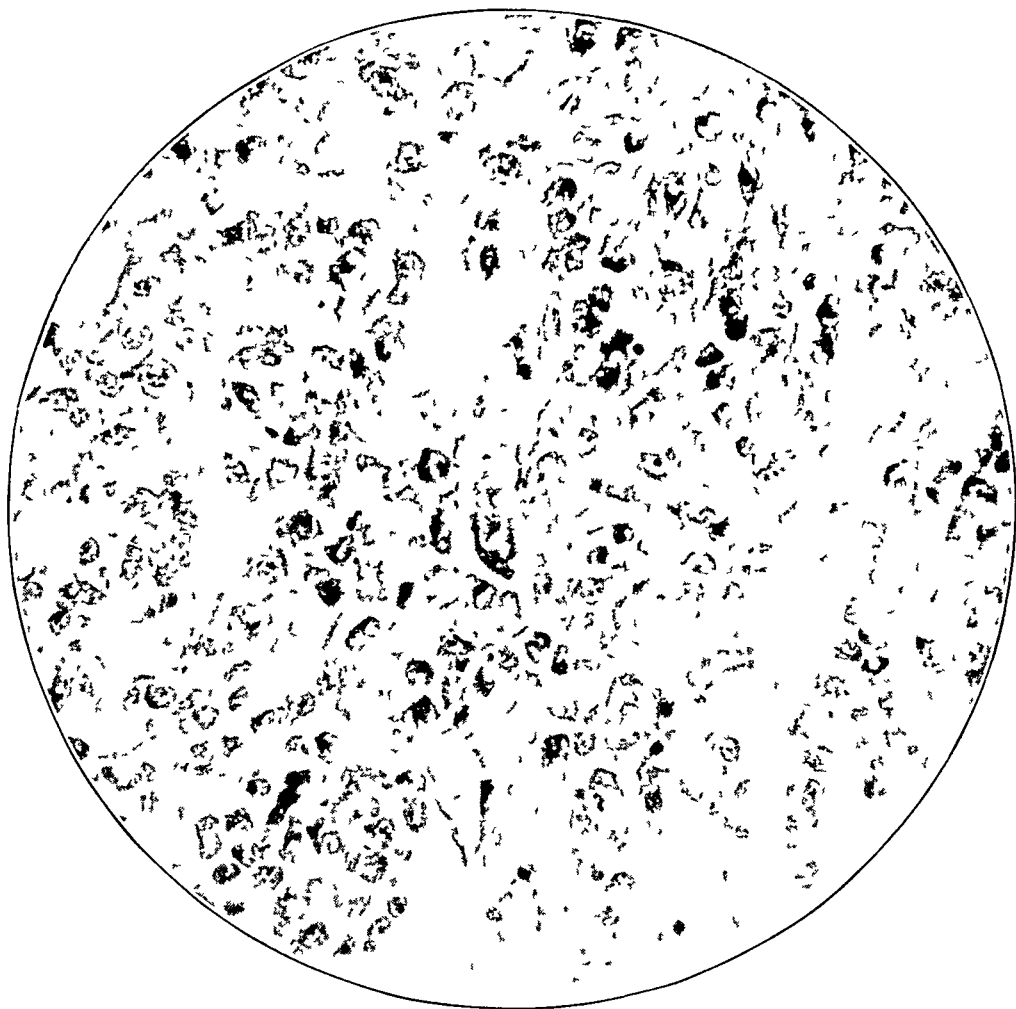


Fig. 5 (case 4) —Carcinomatous metastasis of the heart from a primary parenchymal tumor of the tail of the pancreas

Therapy consisted of supportive measures and the administration of oxygen.

Necropsy—Postmortem examination was performed fourteen hours after death. The heart weighed 175 Gm. The left lateral surface of the parietal pericardium was studded with small tumor nodules. The myocardium was soft, flabby, of poor color and somewhat mottled. There was no gross evidence of metastasis. Histologically the left ventricle was studded with acute milium infarctions. Many of the myocardial branches of the coronary arteries had carcinomatous emboli (fig. 4).

CASE 4—*Carcinoma of tail of pancreas arising from pancreatic parenchyma, metastases to retroperitoneal lymph nodes, lungs and heart*

A white man aged 60, well developed and with evident loss of weight, was admitted to the Second Medical Division, service of Dr O S Wightman, on Oct 31, 1928. The chief complaints, which dated back about three months, were attacks of fainting, a loss of weight of 45 to 50 pounds (20.4 to 22.7 Kg), increasing weakness and some precordial pain and discomfort, particularly on walking. He had been at another hospital for one week before entering the City Hospital. Except for some dulness over the left lower portion of the chest, the findings were essentially negative.

Examination—The heart sounds were weak and of poor quality. The pupils were irregular and reacted sluggishly. There was slight edema of the ankles. There were no other findings of note.

Course—The most prominent features were extreme weakness, low grade fever, the temperature ranging from 98 to 101 F, low blood pressure, 80 systolic and 60 diastolic, tachycardia, and poor quality of the heart sounds. The pulmonary signs varied from time to time. Electrocardiographic examination on November 9 showed normal sinus rhythm, simple tachycardia, a rate of 128, low voltage of all complexes and no axis deviation. The Wassermann reaction of the blood was negative. The urine showed a few pus cells. The blood contained 35 mg of non-protein nitrogen and 100 mg of sugar. Toward the end the pulse became weaker and irregular, with dropped beats. Death occurred on November 2.

Necropsy—Postmortem examination was performed twenty-eight hours after death. The heart weighed 350 Gm. There were two large metastatic nodules in the left ventricle and in the interventricular wall. The histologic picture was that of anaplastic carcinoma (fig 5).

The pancreatic tumor originated in the parenchyma. Islets were preserved within the tumor, and in some there was local invasion of the capillary bed.

REVIEW OF THE LITERATURE

The literature on tumors of the heart and pericardium causing cardiac dysfunction is surprisingly extensive. Perlstein,¹ in 1918, collected 31 cases of primary sarcoma and reported 1 of his own. Mandelstamm,² in 1923, found 1 case not cited by Perlstein and 6 cases of benign tumors. Clerici,³ in 1927, added 23 other cases from the literature previous to 1918. Ludwig⁴ added 8 more in 1933. Since 1918 more than 100 cases have been reported and are briefly summarized in the tables. The *Quarterly Cumulative Index Medicus* lists a few more in the less easily available foreign journals. Probably many other cases have been observed and never reported.

1 Perlstein, I. Primary Sarcomas of the Heart, *Am J M Sc* **156** 214, 1918.

2 Mandelstamm, M. Primary Neoplasms of the Heart, *Virchows Arch f path Anat* **245** 43, 1923.

3 Clerici, C. Tumors of the Heart, *Tumori* **13** 90, 1927.

4 Ludwig, H. Functional Stenosis of the Mitral Valve by Tumor of the Left Auricle, *Ztschr f klin Med* **123** 587, 1933.

TABLE 1—Cases of Primary Benign Tumors of the Heart Reported in the Literature

Author	Sex and Race*	Age, Years	Findings, Course, Duration	Type of Lesion†
Vannucci, D Sperimentale, Arch di biol 77 33, 1923			Hemiplegia, coma, signs of mitral stenosis, recovery, decomposition 1½ months later, marked asthenia, sudden death in 2 weeks	Fibromyoma, LA, with ball valve action
Nowicki, W Virchows Arch f path Anat 259 502, 1926	F	29	Severe dyspnea and congestive failure	Myoma, LA
Binder, A Beitr z path Anat u z allg Path 77 332, 1927	F	45	Congestive failure	Myoma, LA
Schwartz, D Virchows Arch f path Anat 264 747, 1927	F	14	Signs and symptoms of mitral stenosis, 6 or 7 months	Myoma, LA
Emmer, K Deutsches Arch f klin Med 159 164, 1928	F	37	Signs of mitral stenosis, markedly enlarged heart, severe dyspnea, tachycardia, about 1 year	Myoma, LA
Martin, E Ann d'anat path 6 159, 1929	F	66	Long history of dysfunction, diagnosed 15 years previously as mitral stenosis, sudden death	Fibromyoma, LA, with partial obstruction of mitral valve
Houck, G H, and Bennett, G A Am Heart J 5 787, 1930			Fainting on standing, loss of weight, in last week increasing dyspnea, cyanosis, tachycardia, fever, signs of mitral stenosis, cold extremities, abnormal electrocardiogram, sudden death, 6 weeks	Polypoid fibroma, LA
Wassiljeff, A A Frankfurt Ztschr f Path 40 424, 1930	F	43	Long standing cardiac history, severe terminal congestive failure	Myoma, LA
Yater, W M Arch Int Med 48 627 (Oct) 1931 Barnes, A R, and Yater, W M M Clin North America 12 1603, 1929	F	23	Dyspnea, palpitation and weakness, rapid progress in last 6 months, greatly enlarged heart, electrocardiographic changes, 2 years	Pedunculated myoma, LA
Ludwig ⁴	M	34	Slight cyanosis, signs of mitral stenosis	Fibromyoma, LA
Jensen, O R Northwest Med 33 331, 1934	F White	32	Progressive failure, signs of rheumatic heart disease, sudden death	Fibromyoma, LA
Gorlitzer, V Zentralbl f allg Path u path Anat 61 115, 1934	F	50	Severe progressive failure	Myoma, LA
Montaldo, G Arch ital d'anat eistol pat 6 313, 1935	F	51	Weakness, palpitation, greatly enlarged heart	Fibromyoma, LA

Author	Sex and Race*	Age, Years	Findings, Course, Duration	Type of Lesion†
Bien, C W, and Ch'nn, K Y Case M J, 1936, supp, p 61	M	59	Sudden left ventricular failure, periods of improvement, several normal electrocardiograms, sudden death, 3 months	Fibromyoma, LA, protruding into ventricle
Glechrist, A R, and Millar, W J Edinburgh M J 43 213, 1936	M	57	Preordial pain, great exhaustion, arrhythmias, rapid course, congestive failure with persistence of pain, paroxysmal auric ular tachycardia, sudden death with deep cyanosis, 3 months	Myoma, LA
Clerc, A, Gauthier Villars, P, Delamarre, J, and Roge Arch d mal du cœur 30 301, 1937	F	31	Long standing dysfunction, intense cyanosis and dyspnea developing, electrocardiograms showing normal sinus rhythm, a rate of 100-120, Ls, low voltage, T3 and P3 inverted, Q3 notched	Myoma, LA, with ball valve
Riopelle, I L Ann d'anat path 11 725, 1937	F	5	Progressive severe congestive failure, signs of mitral stenosis, 1 year	Myoma, LA, with prolongation into orifice
Benjamin, H J Arch Path 27 930 (May) 1939			Increasing dyspnea, weakness, hemoptysis, fainting, spells, ankle edema, signs of mitral stenosis, pulse deficit, sudden death, 3 weeks	Fibromyoma, LA, with ball valve obstruction
Fossel, M Frankfurt Ztschr f Path 49 355, 1936	F	32	Decompensation with marked ascites for 1 years, peripheral edema and marked systolic murmur	Myoma, LA
Weltmann, O Wien klin Wchnschr 13 537, 1920	F	31	Some cardiac dysfunction since youth, definite dysfunction 4 years with murmurs, one 2 minute attack of asystole	Fibromyoma, RA
Ugrumow, B Centralbl f allg Path u path Anat 41 7, 1927	F	20	General precordial systolic murmur, short tricuspid diastolic murmur, slightly enlarged liver, tachycardia, arrhythmia, greatly enlarged heart, late intense cyanosis, 6 months	Myoma, RA, projecting into RV
Strouse, S Arch Int Med 62 101 (Sept) 1938	F	15	Congestive failure, greatly enlarged heart, 2 months	Papillary myoma, RA
Chirari, H Centralbl f allg Path u path Anat 62 241, 1931	M White	63	Heart disease diagnosed at age of 20, transient decompensation at 48, repeated subsequently, long free periods, increasing severity last year with decreasing reserve, variability of murmurs, constant liver enlargement, death from ruptured intestinal cancer, 13 years	Myoma, RA
Amersbach and Handorn Frankfurt Ztschr f Path 25 121, 1921	F White	32	Decompensation 13 months, sudden death	Massive myoma, right side of heart, with pulmonary embolization
Sikl, cited by Farber, S Am J Path 7 105, 1931	M	7 days	Cyanosis at birth, cardiac failure and death 7th day	Solitary rhabdomyoma of LV and IVW
Brown, G, and Gray, J Lancet 1 915, 1930	M	9 weeks	Clinical diagnosis of valvular disease	Solitary rhabdomyoma
		3 months	Sudden death while crying	Rhabdomyoma

TABLE 1—Cases of Primary Benign Tumors of the Heart Reported in the Literature—Continued

Author	Sex and Race*	Age, Years	Findings, Course, Duration	Type of Lesion†
Berger, L., and Vallee, A. Anat path 7 797, 1930	M	2	Epileptiform attacks, sudden death	Multiple rhabdomyomas of LV and IVW
Reitano, R., and Nucciothi, L. Cuore e circol 17 605, 1935		1 day	Sudden death with intense cyanosis	Multiple rhabdomyomas
Lymburner, B. R. Canad M A J 16 368, 1934	F	15	Stokes Adams syndrome, 3 months	Rhabdomyoma
Ill, C. H., and Gray, J. W. Am J Obst & Gynec 28 204, 1934		2 days	Sudden onset of signs suggestive of cerebral hemorrhage, sudden death 1 hour later	Rhabdomyoma
Wegman, M. E., and Egbert, D. S. J. Pediat 6 818, 1935	F	10 months	Convulsion at 7 months, sudden attacks of pallor, outstanding features cardiac irregularity and tachycardia, electrocardiograms showing normal sinus rhythm, rate 240, tachycardia of auricular flutter	Rhabdomyoma of mitral and tricuspid valves, obliterating bundle of His
Puhl, W. Monatschr f Kinderh 66 22, 1936	M	6 months	Enlarged heart discovered on 5th day, progressive failure from 4th month	Diffuse rhabdomyoma
Elakis, M. Ann de med lég 17 815, 1937	F	10 days	Sudden death	Rhabdomyoma
Rae, M. V. Canad M A J 39 63, 1938	M	3 days	Attacks of cyanosis beginning at 10th hour, persistent by second day, extreme dyspnea, greatly enlarged heart, tachycardia	Multiple rhabdomyomas, LV, RV, IVW, RA
Uehlinger, E. Beitr z path Anat u z allg Path 78 434, 1927	F	14	Enlarged heart, basal murmurs, found dead in bed, 2 months	Lymphangioma
Lloyd, P. C. Bull Johns Hopkins Hosp 44 149, 1929	White	39	Incidental discovery of bigeminal pulse, first degree block, prolonged conduction time, sudden death	Lymphangioma of atrioventricular node
Grant, R. T., and Camp, P. D. Heart 16 137, 1932	White	39	Long standing history of cardiac dysfunction, developing heart block	Hemangioma of lower portion of bundle of His and bifurcation
Perry, O. B., and Rogers, H. J. Path & Bact 39 281, 1934	F	26	Stokes Adams syndrome from age of 4 to 12, recurrence at 26, death during syncope, last period 3 months	Lymphangioma
Kaplan, S. Ztschr f Kreislauforsch 24 565, 1932	M	3½	Cyanosis, enlarged heart, increasing failure, late tachycardia, sudden death, ½ year	Leiomyofibroma of left pulmonary vein, projecting into LA
Neugebauer, W. Zentralbl f allg Path u path Anat 70 2, 1933			Known rheumatic disease of long standing, sudden death	Hamartoma, LV

* M represents male, F, female

† The meanings of the abbreviations in the last column are as follows: LA, left auricle, RA, right auricle, LV, left ventricle, and IVW, interventricular wall

TABLE 2—Cases of Primary Malignant Tumors of the Heart Reported in the Literature

Author	Sex and Race*	Age, Years	Findings, Course, Duration	Type of Lesion†
Gottlieb, L. Deutsche med Wchnschr 74 67, 1919	F	62	Signs of thrombosis of superior vena cava, 9 months	Sarcoma, RA
Lammerich, cited by Clerfay 2	M	70	Cardiac insufficiency	Sarcoma, RV and IVW
Hoffmann, P D Proc New York Path Soc 21 85, 1921	M	37	Incidental discovery of mitral stenosis, decompensation, rapid course, sudden death, 1 month	Pedunculated sarcoma (leiomyoma?), LA, projecting into mitral valve
Cerutti, cited by Clerfay 2	M	45	Progressive cardiac failure	Diffuse lymphosarcoma
Matras, A Ztschr f Kreislaufforsch 19 233, 1927	F	61	Insufficiency numerous murmurs, greatly enlarged heart, sudden death	Diffuse sarcoma
Clerfay 2	F	55	Vertical dyspnea transient edema of legs, enormous heart, marked anemia, intractable course, 1 year	Sarcoma, LA, and pulmonary valve
Diebold O Ztschr f Kreislaufforsch 22 785, 1930	F	55	Cardiac failure, sudden death with severe dyspnea	Sarcoma, RA
Nath, V Indian M Gaz 66 673, 1911	F	50	Moderate general anasarca and intense dyspnea	Sarcoma producing verrucous masses at base of pulmonary valve and myocardium, projecting into artery
Morris, J I J Tab & Clin Med 18 935, 1933	M Negro	15	Sudden death, treated as having cardiac disease for 1½ years	Lymphosarcoma, RA with rupture into pleura and hemothorax
Shelburne, 50 case 1	M Negro	24	Acute decompensation, ascites, rapidly enlarging heart, serous sanguineous pericardial fluid, partial heart block, 10 days	Sarcoma, LA and LV
Case 2	F White	22	Cough, epigastric pain, serosanguineous pericardial fluid, 12 days	Sarcoma, LV and IVW

TABLE 2—Cases of Primary Malignant Tumors of the Heart Reported in the Literature—Continued

Case	Author	Sex and Race*	Age, Years	Findings, Course, Duration	Type of Lesion†
Case 3					
Poujol, G., and Barone, R Assoc franç p l'étude du cancer 26 64, 1937	Bull Moroccan	M White	38 22	Marked dyspnea, anasarca, weak heart sounds, greatly enlarged heart, about 1 month Severe decompensation without obvious cause 2 months	Mesothelioma of pericardium Sarcoma
Popp, L Bull Acad de méd de Roumaine 2 663, 1937		M	33	Chest pain, greatly enlarged heart, temporary improvement with roentgen therapy, recurrence with dyspnea, cyanosis, arrhythmia and congestive failure	Sarcoma
Martin, W C Will, C Am Heart J 17 728, 1939		F	46	Exertional fatigability, dyspnea, anemia and slight loss of weight, progressing to severe congestive failure with slight peripheral edema enlarged liver, harsh murmurs without thrill, cyanosis absent, cardiac area enlarged, electrocardiographic changes, 9 months	Polymorphous cell sarcoma of pulmonary valve, extending into pulmonary arteries
Nowicki, W Anat 259 502, 1926	Virehows Arch f path	F	30	Congestive failure and pericardial rub, 1 months	Fibrosarcoma, LA
Popp 5b		M	32	Onset with chest pain, marked enlargement in roentgenogram, later cyanosis and dyspnea, rapid increase in heart size, transient relief after high voltage roentgen therapy, later congestive failure, 1 months	Fibrosarcoma, RA
Cabot Case 22491, New England J Med 215 1082, 1936		F	33	Substernal oppression and breathlessness for 2 years, last 7 months fever, cough, periodic dyspnea, nonpulsating mass in roentgenogram, increasing rapidly in size, pleural effusion and ascites, 2 years	Fibrosarcoma, RA, projecting into right ventricle
Willius, F A M yo Clin 13 331, 1938	Proc Staff Meet,			Severe congestive failure with dyspnea, cough, dependent edema, massive ascites, weakness, prostration, electrocardiogram showing normal sinus rhythm, rate 67, right axis deviation, T ₁ and T ₂ isoelectric, T ₂ diphasic, 7 or 8 months	Fibrosarcoma, RA, with inferior vena caval obstruction
Godel, A (case 1) u Gefasskr 14 99, 1922	Zentralbl f Heil	M	11	Sudden onset with chest pain, dyspnea, hemoptysis 6 weeks, greatly enlarged heart, sudden death with hemoptysis, about 6 weeks	Spindle cell sarcoma, RA, and in pericardial wall, metastases to lungs and brain

Case 2	Author	Sex and Race*	Age, Years	Findings, Course, Duration	Type of Lesion
Mandelstamm 2					
Peck, C S, and Thatcher, H S Arch Int Med 36 830 (Dec) 1925		M	25	Cardiac insufficiency	Round cell sarcoma of pericardium
Muller, H W Path 36 606, 1928	Frankfurt Ztschr f			Refractive congestive failure, 7 months	Spindle cell sarcoma of pulmonary valve
Holer, F Path 51 212, 1937	Ztschr f	F	15	Onset with abdominal signs, followed by subcutaneous tachycardia, distorted shadow	Metastasizing spindle cell sarcoma, wall of LA, extending into hemopericardium
Bradley, E B, and Maxwell, E S J A M A 91 1552 (Nov) 1928		F	26	Severe decompensation, rapid course, loss of weight and arms, markedly enlarged heart, 2 months	Spindle cell sarcoma, RA
Barnes, Beaver and Snell 54		M White	62	Severe pain in upper left part of chest, swelling of legs 2 or 3 months	Metastasizing spindle cell sarcoma, RA
Reeves, J M, and Michael, P Heart J 11 233, 1936		F	63	Chest pain exertional dyspnea loss of weight, fever, pericardial friction rub, later edema of left arm and legs, arrhythmia, complete block, 1 month	Rhabdomyosarcoma
Schubach, H Path 80 673, 1928		F	16	Exertional fatigability 1 year, last 6 days marked fatigue, abdominal pain, dyspnea, tachycardia, enlarged liver, distant heart sounds	Rhabdomyosarcoma
Lewie, R, and Bauer, R Roman P G Ann Int Med 12 258, 1938		M White	58	Diagnosis of aortic stenosis 1 year before death, final p c cough, dyspnea, enlarged heart, sudden death on exploratory operation	Rhabdomyosarcoma, both auricles, filling both cavities extending to ventricles with rupture
		M White	27	Onset with angina and pericarditis enlarging heart electrocardiographic readings somewhat like those of coronary occlusion, 3½ months	Pedunculated leiomyosarcoma, RV, projecting into main and left pulmonary artery
				LA, left auricle, RA, right auricle, LV, left ventricle, RV, right ventricle, and IVW,	Myosarcoma, RA
					Spindle cell sarcoma of pericardium

* M represents male
 † The meanings of the abbreviations in the last column are as follows
 Interventricular wall

TABLE 3—*Cases of Metastatic Tumors of the Heart Reported in the Literature*

Author	Sex and Race ^a	Age, Years	Findings, Course, Duration	Type of Lesion [†]
Caussade, G., Surmont, J., and Lacapere, J. Bull et mem Soc med d hop de Paris 49 1243, 1925	M	69	Carcinoma of lung developing, increasing paroxysmal dyspnea, edema of legs, intense cyanosis and cardiac enlargement	Carcinoma extending into left side of heart and projecting into auricle
Fishberg, A. M. Am J M Sc 180 629, 1930	M	69	Bronchogenic carcinoma developing, inverted T wave, auricular fibrillation, intense orthopnea and cyanosis	Extension from right bronchus into auricular walls and left auricular cavity
	M	64	Known cancer of lung developing, 8 months later auricular flutter for 2 days, becoming permanent 1 days later with agonizing orthopnea and intense cyanosis	Direct invasion of RA
	M	65	Signs of pressure from mediastinal tumor, frequent angina, transient auricular flutter	
Mead, C. H. J Thoracic Surg 2 87, 1932			Left ventricular failure with severe dyspnea, weakness, cyanosis and tachycardia, death in 24 hours	Sarcoma of cervical nodes with metastases to RA and LV, one surrounding left coronary artery
Matheson, N. M. Brit J Radiol 8 248, 1935			Cough 3 months, dyspnea on exertion, then continuous dyspnea cyanosis, tachycardia enormous cardiac enlargement, serousanguineous pericardial fluid	Bronchogenic carcinoma metastasizing to RA and venous extension through LA into LV
Auerbach, O., Epstein, H. A., and Gold, H. Am Heart J 12 467, 1936	M White	49	Ulcer for 5 months, then hematemeses, later hemoptysis and cardiac angina, electrocardiograms showing auricular flutter, reversion to normal sinus rhythm, with inverted T waves, congestive failure and partial block	Bronchogenic carcinoma with massive myocardial and pericardial involvement
Schmitzer and Bailey ^c			Bronchogenic carcinoma with hemorrhagic pericardial effusion, tumor cells and fluctuant arrhythmias, sudden death	Bronchogenic carcinoma with pericardial metastases and hemorrhagic effusion
Heninger ^{cc}	M White	51	Known cancer of lung developing, marked increase in size of heart, increasing dyspnea and hemorrhagic pericardial fluid with tumor cells	Direct extension to RA
	M White	42	Serohemorrhagic pleural effusion, severe dyspnea, tachycardia, paroxysmal alteration of rhythm, acute cardiac collapse	Pericardial metastases
	M White	55	Loss of weight and weakness 6 months, low blood pressure, tachycardia, subnormal temperature, poor heart sounds	Mesothelioma of pleura with pericardial metastases
Helwig, F. C. J Kansas M Soc 36 265, 1935			Known cancer of lung developing, signs of venous thromboses, edema of face and neck, engorged veins, cyanosis	Carcinoma of kidney
			Known renal cancer with metastases to lung developing, precordial pain, dyspnea and edema (last two symptoms out of proportion to evidence of lung metastases)	
Holt, W. L., Jr. J A M A 102 1921 (June 9) 1934	M White	72	Swelling of neck, severe dyspnea, marked cyanosis of head, neck and right arm	Thyroid carcinoma with extension into great veins, right side of heart and inferior vena cava
Mencarelli, L. Cuore e circolaz 18 533, 1934	M	57	Goiter since childhood, developing malignant growth and lymphatic metastases, excessive cyanosis and edema of arms	Thyroid carcinoma with extension through great vessels to heart
Kapshov, R. Ann Surg 83 161 1926			Radical mastectomy for cancer, 11 months later angina and local recurrence followed by congestive failure and death during uremic attack in 5 months	Direct lymphatic extension to heart and compression of pulmonary vessels and aorta

Author	Sex and Race*	Age, Years	Findings, Course, Duration	Type of Lesion†
Gernez, C.; Breton, A., and Boury, M. Bull Assoc franç p l'étude du Cancer 26 58, 1937	M			
Linell, F. A Brit M J 1 872, 1922		72	Cancer of tongue cured by roentgen therapy, markedly enlarged heart, decided hypotension, weak cardiac sounds	
Vaschaun, W. D. and Heyer, F. W Am J Cancer 24 831, 1935	F	43	Inoperable laryngeal tumor, sudden collapse simulating angina, death in 24 hours	
McNamara, W. L., Ducey, D. F., and Baker, L. A Am Heart J 13 108, 1917	M White	53	Known gastric carcinoma developing, subcutaneous metastases and terminally weak, intermittent pulse	
Culpepper, A. L., and Haam, F. Am J Cancer 21 155, 1934	M White	45	Known rheumatic cardiac congestive failure and anginal attacks	
Darnall, F. R. Mil Surgeon 81 325, 1917	Negro	56	Ascites and edema of legs, sudden cardiac failure	
Mumada, J. C. Semana med 1 1766, 1927	M White	56	Intestinal symptoms 4 months, sudden left ventricular failure, auricular fibrillation, pulse deficit, irregular blood pressure, all symptomless, then precordial fullness and fluttering, exhaustion, air hunger, gallop rhythm, 40 hours	
Rist, I., and Rolland, J. Ann de med 1: 538, 1923	F	40	Known cancer of vulva, with terminal 4 day period of increasing dyspnea, sudden death	
Scott and Garvin	F		Four years after operation for cervical cancer syndrome of pulmonary tuberculosis and tachycardia	
			Cancer of bronchus with cardiac failure and hemorrhagic pericardial effusion	
			SA cases of myocardial failure, half with recognized tumor and paroxysmal auricular fibrillation, half with unrecognized tumor and paroxysmal auricular fibrillation	
Pinnell, L. G. Canad M A 1 1: 108, 1923	M		Cancer of bronchus with paroxysmal auricular fibrillation, no failure	
Rosco, G. Semana med 31 804, 1924	F		Cancer of bronchus with auricular tachycardia	
Roesler, O. Zentralbl f Herz u Lungen 16 211, 1924		17	Melanoma of eye with several attacks of paroxysmal fibrillation	
Krumpholtz, E. B., and Crowell, C. Am J M Sc 170 828, 1925	M		Congestive failure, enlarged mediastinal shadow, hemorrhagic pleural fluid, 3 months	
Carnot, P., and Lambing, A. Bull et mém Soc méd d hóp de Paris 52: 1773, 1923		47	Known mediastinal tumor developing, tachycardia, auricular extrasystoles and pericardial fluid with tumor cells	
Chir 1 37, 1923 1929	F White	43	Sarcoma of finger, amputation, deltoid metastases in 10 months, then angina, decompensation, heart block, 1 month	
			Metastatic melanoma with spontaneous rupture of heart	
			Course suggestive of subacute bacterial endocarditis, 7 months	
				Sarcoma of stomach, metastasizing to liver and then to heart

TABLE 3—Cases of Metastatic Tumors of the Heart Reported in the Literature—Continued

Author	Sex and Race*	Age, Years	Findings, Course, Duration	Type of Lesion†
Willius and Amberg ^{5a}	F	8	Ewing sarcoma of femur, 5 months later increasing periods of tachycardia, dyspnea, weight loss, then cyanosis, exertional dyspnea, easy fatigability, greatly enlarged heart, incomplete bundle branch block, congestive failure, 16 months Leukemia with extreme dyspnea	Almost entire RV Diffuse involvement
Siegel, M. L., and Young, A. M. Am Heart J 8 682, 1933	M White	47	Gastrointestinal symptoms, weak heart sounds, constantly inverted T waves and lack of reciprocal direction in leads 1 and 3	Retropéritoneal lymphosarcoma
Johns, E. P., and Sharpe, W. C. Am J Cancer 23 45, 1935	M	18	Blood stained expectoration, frequent hemoptysis, rapid emaciation, marked dyspnea, frequent attacks of cyanosis, hemothorax, 3 months	Sarcoma of lung, with venous extension to LA and mitral obstruction
Films, R. W. B. Proc Roy Soc Med 28 667, 1935	F	8	Paroxysmal cough, later dyspnea, pleural effusion and greatly enlarged heart	Thymic lymphosarcoma with pericardial metastases
Polka, J. A., and Gogol, L. J. Am J Cancer 27 329, 1936	M Mexican	49	Stupor greater than usual in cardiac disease, to and fro murmur, low blood pressure, hemorrhagic pleural effusion, partial block, sinus arrhythmias	Carcinoma of kidney with sarcomatous metastases
Smith ^{5b}			Abdominal malignant lesion with increasing dyspnea, greatly enlarged heart, inverted T waves in all leads abnormally small QRS	Sarcoma of liver
Doane and Solis Cohen ^{5c}	M White	62	Enucleation of eye for melanoma, pallor, dyspnea precordial friction rub, marked cardiac enlargement	Multiple metastases
Wainwright, C. W. Bull Hopkins Hosp 63 187, 1938	F White	51	Pelvic tumor developing, auricular flutter with dyspnea, enlarging heart, fixed right cardiac border, variable electrocardiogram, coronary thrombosis, flutter, block Amputation for sarcoma of tendon sheath, pulmonary metastases in 5 years, 1 months later increasing palpitation, dyspnea, greatly enlarged heart, signs of mitral stenosis, death following thoracotomy	Neuroblastoma of adrenal glands metastases to RA Metastases from lung to LA and venous extension into LA, obstruction of mitral valve
	F Negro	42	Physical signs of mitral stenosis	Sarcoma of uterus with tumor thromboses of veins and extension through tricuspid and pulmonary valves
McDonald, S., Jr., and Heather, J. C J Path & Bact 48 533, 1939	M	52	Amputation of leg for myeloid reticulosarcoma, metastases to lung 8 years later, in 6 months congestive failure, displaced heart loud sounds at mitral valve, accentuated pulmonary and aortic sounds Pulmonary signs with slight congestive failure, transient improvement, then recurrence, progressive dyspnea, edema of legs, orthopnea, slight cyanosis, variable apical systolic murmur, sudden death, 5 or 6 months	Venous extension from pulmonary metastases into LA and through mitral valve Primary rhabdomyosarcoma of lung with venous extension into LA and through mitral valve

* M represents male, F, female

† The meanings of the abbreviations in the last column are as follows LA, left auricle, RA, right auricle, LV, left ventricle, RV, right ventricle, and IVW, interventricular wall

COMMENT

It is admittedly difficult correctly to diagnose neoplasms of the heart, chiefly because no single person observes many cases and also because the presence of such lesions is seldom considered a possibility. The onset of cardiac dysfunction when a malignant tumor in some other organ has been recognized or intractable cardiac dysfunction of obscure cause is present should make one suspect the presence of tumor. Roesler, in 1924, made the first correct clinical diagnosis. Fishbeig was the first to report it in the American literature, in 1930. Since then there have been several other correct clinical diagnoses.⁵ Roesler's case was one of a metastatic tumor. To Popp^{5b} (1932) is due the credit for the first correct diagnosis of a primary tumor, and in this country to Barnes, Beaver and Snell^{5d}.

The syndromes observed have simulated those due to most of the recognized causes of heart disease. The signs and symptoms seem caused more by the location than by the character of the neoplasm. The malignant tumors, however, modify the manifestations. The following outline of manifestations is merely suggestive, since bizarre combinations appear more frequently than the clearcut pictures.

- 1 Intractable myocardial insufficiency
- 2 Serosanguineous pericardial effusion
- 3 Valvular diseases, usually mitral stenosis
- 4 Coronary disease, angina or its equivalents
- 5 Stokes-Adams syndrome
- 6 Arrhythmias
- 7 Venous thrombosis
- 8 Sudden death with or without preceding symptoms
- 9 Banal symptoms

5 (a) Willius, F. A., and Amberg, S. Two Cases of Secondary Tumors of the Heart in Children, *M. Clin. North America* **13** 1307, 1930. (b) Popp, L. Tumors of the Heart, *Fortschr. a. d. Geb. d. Röntgenstrahlen* **46** 23, 1932. (c) Hemminger, B. R. Clinical Aspects of Pericardial Metastases, *Ann. Int. Med.* **7** 1359, 1934. (d) Barnes, A. R., Beaver, D. C., and Snell, A. M. Primary Sarcoma of Heart. Case with Electrocardiographic and Pathological Studies, *Am. Heart J.* **9** 480, 1934. (e) Shelburne, S. A. The Diagnosis of Tumors of the Heart and Pericardium, *Texas State J. Med.* **31** 433, 1935. Primary Tumors of the Heart with Special Reference to Certain Features Which Led to Logical and Correct Diagnosis Before Death, *Ann. Int. Med.* **9** 340, 1935. (f) Doane, J. C., and Solis-Cohen, L. Symmetrical Adrenal Neuroblastoma Metastasizing to the Right Auricle, *J. A. M. A.* **109** 578 (Aug. 21) 1937. (g) Schnitker, M. A., and Bailey, O. T. Metastatic Tumor of the Heart. Case Diagnosed During Life, *ibid.* **108** 1787 (May 22) 1937. (h) Smith, D. S. Neoplastic Involvement of the Heart. Two Cases Diagnosed Before Death, *ibid.* **109** 1192 (Oct. 9) 1937. (i) Scott, R. W., and Garvin, C. F. Tumors of the Heart and Pericardium, *Am. Heart J.* **17** 431, 1939.

The refractory character of the decompensation noted in case 1 has been stressed by many observers. It has frequently been the outstanding feature. All of the known procedures appear to have no beneficial effect, or at most a transient and minor one. The sarcomas appear particularly prone to acquire this character to a striking degree. In several of the cases of myxoma or fibromyxoma of the auricles it has also been shown. It is unusual as the main manifestation of other tumors.

Serohemorrhagic pericardial effusion with extreme rapidity of recurrence after removal was a striking feature in case 1. Shelburne^{5c} noted the same feature in 2 of his cases and stressed its importance in the diagnosis of neoplasm. Heninger^{5d} stated that its presence indicates pericardial involvement by metastatic growths. It has not been reported frequently and has been found with primary sarcomas and pericardial tumors metastatic from the lungs. In our case it was associated with a metastatic lymphosarcoma. Tumor cells were found in the cases of Heninger^{5c} and of Schnitker and Bailey^{5g}. Occasionally the pericardial effusion was associated with pleural effusion of the same character.

Rheumatic heart disease was considered in the differential diagnosis in our first case. Most of the observers said they believed it the most likely diagnosis throughout the course in spite of the features unexplainable on this ground. In several cases recorded, including those of both primary and secondary and benign and malignant lesions, the same question in diagnosis had arisen. In the majority, the previous history revealed nothing suggestive of rheumatic disease. In our own case, head colds and sore throat were of frequent occurrence, giving a possible background for the development of that disease. The existence of rheumatic heart disease, however, seemed unlikely, since the patient had been able to carry on strenuous exercise without cardiac embarrassment as recently as the previous summer.

The tumor which has given a picture most closely resembling that of the rheumatic heart has been the myxoma or fibroma of the left auricle. In about half of the cases collected the signs of mitral stenosis were found. In a few cases it was noted that the character of the murmur was variable and related to positional changes. A pedunculated sarcoma of the left auricle reported by Hoffmann gave physical findings similar to those of the benign tumors of the same chamber. In the metastatic sarcomas of Wainwright the same signs were produced.

Simulation of other valvular defects was unusual. In Siki's case, in which the condition was diagnosed clinically as valvular disease, there was a rhabdomyoma. In Weltmann's case the signs of tricuspid stenosis were present, the myxoma was in the right auricle.

Symptoms similar to those of coronary sclerosis were prominent in cases 2 and 3. As in cases of this condition, the tumors producing them

were usually metastatic and the symptoms frequently terminal phenomena. Primary tumors have infrequently been associated with angina.

The Stokes-Adams syndrome was infrequently observed and found only in association with rhabdomyoma and angioendothelioma of the bundle of His. Ball valve action of pedunculated tumors of the left auricle sometimes caused sudden collapse simulating the Stokes-Adams syndrome.

Arrhythmias were frequent, and the striking feature was the rapidity with which they fluctuated. Of the many cases in which electrocardiographic studies were done, in only 1, that of a myxoma of the left auricle reported by Bien and Ch'in, was there a consistently normal tracing.

Thrombosis of the large veins occurred usually from prolongation of the tumor through veins from distant sources, occasionally in cases of malignant tumors of the right auricle. Jacobi and Seltzer⁶ made the interesting observation that carcinoma of the thyroid causes cardiac dysfunction only by extension through the veins into the right side of the heart and that true metastases from this organ are unassociated with it. This proved to be the mechanism in the only 2 cases of cancer of the thyroid found in this review, the cases of Holt and Mencairelli.

Sudden death was unusually common, occurring in 29 of the reported cases. It occurred more frequently in the cases of primary than in those of metastatic tumors. Of the 24 cases of fibroma or myxoma of the auricles, sudden death occurred in 8 (or one third of the cases). In 3 of the 4 cases of angioendothelioma death was also sudden. There were 2 sudden deaths in the 11 cases of rhabdomyoma. It was of interest to note that of the 5 cases of primary sarcoma in which the patient died suddenly, in 4 the right auricle was involved. Of the cases of metastatic tumors, there was sudden death in only 4. Auricular involvement was present in 2 cases in which sudden death was the result, and in 1 such case the myocardial location was unspecified. In the last case, that of McDonald and Heather, malignant venous propagation had caused mitral obstruction.

Only banal symptoms were present in case 4. This complex occurred in only a small number of cases and was characterized by low blood pressure, marked tachycardia and poor quality of the heart sounds.

Dyspnea was frequent and usually intense. Occasionally it was the most prominent feature. Sometimes it was described as agonizing. Cyanosis was not always present, but when it occurred tended to be extreme. Tachycardia, frequently marked, was noted almost invariably. Loss of weight and anemia were important findings in several cases. As would be expected they were more frequently prominent among the

6 Jacobi, M. and Seltzer, J. Cardiac Metastases from Carcinoma of the Thyroid, *Am Heart J* 12: 473, 1936.

cases of metastatic tumors. In case 1 loss of weight was an important finding leading to the correct diagnosis and was in sharp contrast to the findings in other cases of cardiac decompensation in patients under observation in the ward at the same time.

The roentgenologic studies gave one finding almost invariably, the extreme enlargement of the cardiac shadow. Occasionally this enlargement was the first observation noted. In a few cases, there was fixation or irregularity of individual contours.

Bizarre combinations of signs and symptoms seem to dominate in many cases. In the cases of myxoma of the left auricle transient interference with the peripheral circulation and signs of mitral stenosis have been observed. There have been attacks of fainting on standing and short periods of cold cyanosis of the extremities. The murmurs have been found variable, sometimes soft and at other times typical of stenosis. The electrocardiographic tracings, although abnormal, have not shown the features usually seen accompanying the rheumatic heart. In the case of Bien and Ch'in, the clinical syndrome of sudden left ventricular failure was associated with normal electrocardiographic tracings. Gilbert and Millar's patient had paroxysmal rhythms following congestive failure.

In the cases of malignant primary tumor the signs of severe cardiac failure have been present in the absence of peripheral edema and ascites. Frequently there has been intense dyspnea with no orthopnea. Severe dyspnea and a low value for the carbon dioxide-combining power of the blood have been observed in the absence of cyanosis.

In the cases of metastatic growth one of the most striking features has been the changes in rhythm, tending to be fluctuant. In association with recognized metastases to other organs, the cardiac symptoms have been out of proportion to the extent of the metastases. There have been low blood pressure readings accompanied with surprising comfort of the patient, as in case 4.

There are many diagnostic features which suggest the presence of tumor. Intractable cardiac dysfunction in the absence of obvious cause is the most common. Extremely large size of the heart, obscure in origin, also is important. The combination of contradictory signs and symptoms has been frequently observed. Serohemothagic pericardial effusion is a most valuable sign. Jensen stressed the effect of postural changes on murmurs. Cardiac failure and arrhythmias in the presence of a known primary malignant growth should arouse suspicion. The roentgen studies usually reveal a large cardiac shadow, sometimes with distortion. Siegel found the lack of reciprocal direction of the T waves in electrocardiographic tracings to be of value.

SUMMARY AND CONCLUSIONS

Four cases of metastatic tumors of the heart causing cardiac dysfunction are reported, and the literature is reviewed

The outstanding feature of cardiac tumors has been the intractable failure without obvious cause. The appearance of cardiac failure or arrhythmia in association with a known malignant growth in some other organ should lead one to consider the possibility of metastasis to the heart. Roentgenologic and electrocardiographic studies are valuable aids

IODINE AND CHOLESTEROL METABOLISMS IN PATIENTS WITH PRIMARY MYXEDEMA

A CLINICAL AND EXPERIMENTAL STUDY WITH A REPORT OF
RESULTS OF TREATMENT

ARTHUR M GREENE, M D

OMAHA

The clinical signs and symptoms of myxedema are well known. However, prior to the last decade too little attention was directed to the biochemical processes of the disease. Hypothyroidism presumably results from a relative or an absolute deficiency of thyroid secretion. Since iodine comprises about 65 per cent of thyroxin, it would appear that further investigation of the metabolism of iodine as evidenced by the iodine levels of the blood and urine is indicated.

A characteristic alteration of the plasma cholesterol is found in patients with thyroid deficiency. This aspect has been investigated by several workers both before and after treatment with desiccated thyroid. The results of these investigations have shown that the level of the cholesterol in the blood is of value in the differential diagnosis of borderline cases of hypothyroidism.

This study had as its purpose the following determinations:

- 1 The level of the iodine in the blood and the urinary excretion of iodine in thyroid deficiency states
- 2 The variation from the normal of the level of the iodine in the blood that might be characteristic of this endocrine disorder, and hence of diagnostic value
- 3 The possible correlation between the level of iodine and that of cholesterol in the blood in cases of thyroid deficiency
- 4 The levels of iodine and of cholesterol in the blood in cases of this condition after the administration of thyroid preparations
- 5 The reaction of the blood iodine and the blood cholesterol in hypothyroidism to the administration of both organic and inorganic iodine compounds. This was studied for the purpose of determining whether

From the Lahey Clinic, Boston. A thesis submitted to the Faculty of the Graduate School of Medicine of the University of Pennsylvania in partial fulfillment of the requirements for the degree of Master of Medical Science (M Sc, Med) for graduate work in internal medicine.

the chemical changes in the blood in the patients receiving thyroid preparations were due to the specific substance or to nonspecific iodine

With the foregoing ideas in mind, the cases of 9 patients with spontaneous, untreated myxedema were investigated. All patients were hospitalized for a period of four to fourteen days. They were then discharged from the hospital and examined at the Lahey Clinic. The clinical course and the chemical alterations in the blood were observed at specific intervals for a period of from one to seven months.

While the patients were in the hospital, the clinical course was closely followed. Frequent estimations of the basal metabolic rate were done, changes in weight were noted, and fluid intakes and outputs were recorded for twenty-four hour periods. The iodine and cholesterol levels in the blood were estimated at intervals of twenty-four to forty-eight hours. The total iodine in the blood and the organic and inorganic iodine fractions were determined. Daily excretion of iodine in the urine was estimated.

The method described by Perkin¹ was used for the biochemical analysis of the total iodine in the blood and urine. The alcohol-precipitable iodine was determined for the estimation of the so-called organic iodine fraction, the alcohol-soluble iodine, for the estimation of the so-called inorganic iodine fraction.²

After the initial clinical, metabolic and biochemical status of each patient was determined, the following courses of treatment were instituted. Three patients were given 1 gram (0.065 Gm.) and 1 patient 2 grams (0.13 Gm.) of U. S. P. desiccated thyroid daily by mouth. Three patients were given daily intravenous injections of thyroxin, the amount of which was biologically equivalent to 1 gram of desiccated thyroid administered orally. One patient was given compound solution of iodine U. S. P. and 1 patient potassium iodide daily, the iodine content of each preparation being approximately ten times that present in 1 gram of U. S. P. desiccated thyroid. On discharge from the hospital, all patients were given 1 gram of desiccated thyroid daily.

Tables 1 to 9 represent the results obtained in each patient.

ANALYSIS OF RESULTS

Plasma Cholesterol—The results of the study of the plasma cholesterol in cases of thyroid deficiency before and after therapy with thyroid preparations have corroborated the findings of other investigators.

1 Perkin, H. J. Determination of Iodine in Blood, *Biochem. J.* **27** 1078-1081, 1933.

2 Perkin, H. J., and Hurvath, L. M. Fractionation of the Iodine of the Blood in Thyroid Disease. *J. Clin. Investigation* **18** 733-739 (Nov.) 1939.

Epstein and Lande³ were the first to stress the diagnostic significance of the elevated level of cholesterol in the blood in hypothyroidism. Hurxthal and Hunt⁴ confirmed this and, in addition, demonstrated that a reciprocal relationship existed between the height of the plasma cholesterol and the lowering of the basal metabolic rate (based on average values for a group of patients). Hurxthal stated that the level of cholesterol in the blood is a better index of thyroid deficiency than the basal metabolic rate. Boyd and Connell,⁵ Bronstein⁶ and others have con-

TABLE 1—*Data from Study of the Iodine and Cholesterol Metabolisms in Patient 1**

Date	Basal Meta- bolic Rate, Per centage	Plasma Choles- terol, Mg / 100 Cc	Whole Blood, Total Content of Iodine, Micro grams/ 100 Cc	Whole Blood, Con- tent of Organic Iodine, Micro grams/ 100 Cc	Whole Blood, Content of Inor- ganic Iodine, Micro grams/ 100 Cc	Fluid Intake, Cc	Fluid Output, Cc	Iodine Excretion in Urine (24 Hr), Mg	Medi- cation, Desic- cated Thyroid	Weight, Pounds
10/ 7/38	-25	362	4.2 4.0	2.0 2.0	2.2 2.0	1,620				115½
10/ 8/38	-21	358	7.2	2.0	5.2	2,280	1,250	0.026	1 gr	114½
10/ 9/38						3,000	2,950	0.062	1 gr	
10/10/38			14.4	1.6	9.8	2,850	2,750	0.058	1 gr	
10/11/38		293	11.7	4.2	7.5	2,550	1,760	0.162	1 gr	
10/12/38						2,340	3,200	0.269	1 gr	
10/13/38		319	6.0	4.4	1.6	3,360	3,150	0.202	1 gr	
10/14/38	-27					3,000	2,800	0.282	1 gr	115
10/15/38	-28	262	11.3	4.2	7.1	2,250	3,100	0.307	1 gr	116
10/16/38						2,700	1,420	0.596	1 gr	
10/17/38	-19	265	7.5	4.2	3.3	2,160	2,900	0.122	1 gr	111½
10/18/38						2,400	2,200	0.202	1 gr	111½
10/19/38	-13	298	9.6	4.2	5.4	2,400			1 gr	111½
10/20/38							3,750	1.827	1 gr	
10/21/38	-13	275	5.1	2.1	3.0		2,350	0.148	1 gr	111¾
10/22/38	- 1	203	8.7	6.0	2.7		530 (incom- plete)	0.175 (incom- plete)		113
2/21/39	+19	222	12.6	8.4	4.4		450 (incom- plete)	0.076 (incom- plete)	1 gr	115¾

* Patient 1—A man aged 60 had spontaneous myxedema of forty years' duration. There were the classic clinical signs and symptoms of myxedema except that the patient was slightly underweight, bradycardia was observed (pulse rate 36 to 50 beats per minute).

Result—An excellent clinical response to relatively small doses of desiccated thyroid was obtained.

3 Epstein, A. A., and Lande, H. Studies on Blood Lipoids (Relation of Cholesterol and Protein Deficiency to Basal Metabolism), *Arch Int Med* **30** 536 (Nov.) 1922

4 Hurxthal, L. M. Blood Cholesterol in Thyroid Disease (Effect of Treatment), *Arch Int Med* **52** 86-95 (July) 1933, Blood Cholesterol and Thyroid Disease (Myxedema and Hypercholesterolemia), *ibid* **53** 762-781 (May) 1934. Hurxthal, L. M., and Hunt, H. M. Clinical Relationships of Blood Cholesterol, with a Summary of Our Present Knowledge of Cholesterol Metabolism, *Ann Int Med* **9** 717-727 (Dec.) 1935

5 Boyd, E. M., and Connell, W. F. Plasma Lipoids in Diagnosis of Mild Hypothyroidism, *Quart J Med* **6** 467-471 (Oct.) 1937

6 Bronstein, I. P. Blood Cholesterol in Cretinism and Hypothyroidism in Childhood, *J. A. M. A.* **100** 1661-1663 (May 27) 1933

curred in these findings Hurxthal also suggested that the level of the cholesterol in the blood plasma may be used as an index to evaluate the amount of thyroid required during the course of treatment He also pointed out that one should not be oblivious to the clinical analysis of the patient which is the best criterion in both diagnosis and treatment

Eight of the 9 patients studied had typical cases of myxedema and had an elevation of the level of plasma cholesterol The average level before treatment was 399 mg per hundred cubic centimeters of blood The range of normal by the method used⁷ was estimated to be from

TABLE 2—*Data from Study of the Iodine and Cholesterol Metabolisms in Patient 2**

Date	Basal Meta- bolic Rate, Per- centage	Plasma Choles- terol, Mg / 100 Cc	Whole Blood, Total Content of Iodine, Micro- grams/ 100 Cc	Whole Blood, Con- tent of Organic Iodine, Micro- grams/ 100 Cc	Whole Blood, Content of Inor- ganic Iodine, Micro- grams/ 100 Cc	Fluid Intake, Cc	Fluid Output, Cc	Iodine Excretion in Urine (24 Hr), Mg	Medi- cation, Desic- cated Thyroid	Weight Pounds
10/15/38		363				720	660			
10/16/38	—39					1,140	990			175½
10/17/38		322	3.1	0.15	2.95	1,260	700	0.088	2 gr	
10/18/38						1,140	950	0.092	2 gr	
10/19/38		307	5.1	2.2	2.9	1,200	600	0.114	2 gr	
10/20/38						1,200	750	0.063	2 gr	
10/21/38	—35	297	3.5	3.3	0.2	1,500	1,530	0.237	2 gr	178¼
10/31/38		225							2 gr	175¾
11/14/38		138	12.6						2 gr	176
12/12/38		124	7.5	6.8	0.7				2 gr	169
1/17/39		157	3.6						2 gr	

* Patient 2—A woman aged 61 had spontaneous myxedema of eight years' duration. Classic signs and symptoms were observed with associated severe arteriosclerosis, cardiac enlargement, a blood pressure of 170 systolic and 96 diastolic and relatively severe mental deterioration of arteriosclerotic origin. Inadequate treatment was given from May 1932 to May 1938. There was no treatment for five months before study was begun.

Result—Three months after treatment with small doses of thyroid was begun right hemiplegia developed, probably from thrombosis of a cerebral artery.

120 to 250 mg per hundred cubic centimeters, with a mean average of 180 mg. The plasma cholesterol decreased as the lowered basal metabolic rate rose to normal in association with clinical improvement. At the termination of the study all the patients had a normal level of plasma cholesterol.

In the exception to the foregoing results, patient 3 (table 3), a woman of 20 with compensated myxedema, the level of blood cholesterol was normal and was not influenced by the administration of thyroxin intravenously or desiccated thyroid orally. This result was in keeping with the normal basal metabolic rate and the absence of clinical signs and

7 Bloor, W. R. The Determination of Small Amounts of Lipid in Blood Plasma, *J Biol Chem* **77** 53-74 (April) 1928.

symptoms of myxedema. The stunted physical development and mental changes in this woman were presumably the result of prolonged thyroid deficiency during the period of development. The hypometabolism had apparently been compensated by a large colloid adenomatous goiter. The goiter decreased in size during thyroid therapy. The thyroid gland had presumably hypertrophied to a degree necessary to maintain normal

TABLE 3—Data from Study of the Iodine and Cholesterol Metabolisms in Patient 3

Date	Basal Metabolic Rate, Per centage	Plasma Cholesterol, Mg/100 Cc	Whole Blood, Total Content of Iodine, Micro grams/100 Cc	Whole Blood, Content of Organic Iodine, Micro grams/100 Cc	Whole Blood, Content of Inorganic Iodine, Micro grams/100 Cc	Fluid Output,† Cc	Iodine Excretion in Urine (24 Hr.), Mg	Medication, Thyroxin Intra venously	Weight, Pounds
10/24/38	+12	160	3.2	2.9	0	1,100	0.074		97½
10/25/38	+ 8	180	5.0	5.0	0	700	0.073	0.33 mg	97
10/26/38	+10	174	2.5	2.1	0	600	0.050	0.33 mg	96
10/27/38	+12	185	18.5	2.1	16.1	725	0.106	0.33 mg	96
10/28/38	+ 7	176	10.6	7.5	3.3	750	0.031	0.33 mg	95
10/29/38	+ 9	163	2.6	2.2	0	825	0.140	0.33 mg	94¾
								Desiccated Thyroid	
11/29/38	+16	188	9.0	3.8	5.1	720 (incomplete)	0.51 (incomplete)	1 gr	100½
3/ 1/39	+29	188	14.5	10.6	4.2	300 (incomplete)	0.057 (incomplete)	1 gr	102¼
5/29/39	+20	153	6.3			320 (incomplete)	1.76 (incomplete)	1 gr	103¾

* Patient 3—A woman aged 20 (sister of patient 4) had juvenile myxedema of unknown duration, compensated from a metabolic standpoint at the time of study by a large colloid adenomatous goiter with a substernal extension. She presented stunted growth, but normal bone age was revealed by roentgenographic study of the epiphyses. Her menses were irregular and scanty but she had normally developed secondary sex characteristics. Mental retardation was shown. Skin texture, hair and tongue presented none of the characteristics of thyroid deficiency. This patient served as a metabolically normal control for the other typically hypothyroid patients.

Result—After seven months of treatment with small doses of thyroid the goiter decreased in size, and the greatest diameter of the neck (over the goiter) diminished 1¾ inches (4.45 cm.) no other improvement was noted.

† Data on fluid intake are incomplete.

metabolism successfully, but when the demands on it were lessened by the therapeutic administration of thyroid, this compensatory hypertrophy was no longer required and partial atrophy resulted. This patient served as a metabolically normal control for the 8 patients with typical hypothyroidism studied.

Patient 8 (table 8) demonstrated that medication with inorganic iodine (compound solution of iodine U. S. P.) had no influence on the plasma cholesterol. The effect of iodine on the cholesterol metabolism in this instance of myxedema thus appeared to be specific only for the organic iodine present in thyroid substance.

Iodine—Analysis of the determinations of iodine in the blood is subject to many misinterpretations. To evaluate fully the iodine metabolism of a given patient the following criteria should be established:

1 The content of iodine ingested in food, as well as any form of medication with iodine, should be known. A sea food dinner or the use of iodized salt on food will appreciably elevate the iodine in the

TABLE 4—Data from Study of the Iodine and Cholesterol Metabolisms in Patient 4^{*}

Date	Basal Meta- bolic Rate, Per- centage	Plasma Choles- terol, Mg / 100 Cc	Whole Blood, Total Content of Iodine, Micro- grams/ 100 Cc	Whole Blood, Content of Organic Iodine, Micro- grams/ 100 Cc	Whole Blood, Content of Inor- ganic Iodine, Micro- grams/ 100 Cc	Fluid Output, [†] Cc	Iodine Excretion in Urine (24 Hr.), Mg	Medication, Thyroxin Intra- venously	Weight, Pounds
10/24/38	-25	337	6.0	4.2	2.2	650	0.137		94
10/25/38	-36	368	5.0	5.0	0	375	0.028	0.33 mg	94½
10/26/38	-34	323	5.6	3.3	2.1	900	0.064	0.33 mg	93¾
10/27/38	-23	318	6.2	4.2	1.8	700	0.088	0.33 mg	93½
10/28/38	-19	263	9.4	8.4	1.38	825	0.049	0.33 mg	94
10/29/38	-16	308	6.2	4.2	2.2	450 (incomplete)	0.047	0.33 mg	93
11/29/38	-8	150	11.4	7.5	4.4	870 (incomplete)	0.183	1 gr	85
3/1/39	+4	204	5.2	2.1	3.0	415 (incomplete)	0.070	1 gr	75¾
5/29/39	+6	164	33.8			600 (incomplete)	0.050	2½ gr	72½

* Patient 4—A boy aged 14 (brother of patient 3) had juvenile myxedema of nine or ten years' duration. Apparently development was normal to the age of 4 or 5 years. He presented a great excess in weight and skin, hair, tongue and fat distribution were typical of hypothyroidism. Bone age was 4 years, determined by roentgenographic study of the epiphyses. Mental retardation was moderate. A small substernal thyroid was revealed in roentgenograms. Infantile genitalia with cryptorchidism were observed.

Result—After seven months of treatment, the boy had lost 21½ pounds (9.7 Kg.), the height had increased 3½ inches (8.9 cm.), the testes had enlarged and entered the scrotum, the skin, hair and tongue had changed to normal appearance and the mentality had improved.

† Data on fluid intake are incomplete.

blood.⁸ External contacts with iodine (such as the application of iodine to the skin) should also be eliminated.

2 The patient should be in a state of physical and emotional rest at the time blood is taken for analysis. Exertion may elevate the level of iodine in the blood.⁹

8 Curtis, G. M. Iodine Relationships of Thyroid Disease, Surg., Gynec. & Obst. **62** 365-372 (Feb.) 1936.

9 (a) McCullagh, D. R. Hypothyroidism. Studies of Blood Iodine by Use of New Chemical Method (Diagnostic Application), Cleveland Clin. Quart. **2** 15-37 (Jan.) 1935. (b) Perkin, H. J., Brown, B. R., and Lang, J. Iodine Tolerance Test of Normal and Thyrotoxic Individuals, Canad. M. A. J. **31** 365-368 (Oct.) 1934.

3 In women, the stage of the menstrual cycle should be known, as a premenstrual rise in the iodine of the blood may occur¹⁰

4 Blood should be drawn for estimations of iodine at a definite period after thyroid therapy In the present study all blood was obtained from twenty to twenty-four hours after iodine was administered

5 Excretion of iodine in the feces should be estimated

6 The content of iodine in complete twenty-four hour specimens of urine should be known

TABLE 5—*Data from Study of the Iodine and Cholesterol Metabolisms in Patient 5**

Date	Basal Meta- bolic Rate, Per centage	Plasma Choles- terol, Mg / 100 Cc	Whole Blood, Total Content of Iodine, Micro grams/ 100 Cc	Whole Blood, Con- tent of Or- ganic Iodine, Micro grams/ 100 Cc	Whole Blood, Content of Inor- ganic Iodine, Micro grams/ 100 Cc	Fluid Intake, Cc	Fluid Output, Cc	Iodine Excretion in Urine (24 Hr.), Mg	Medi- cation, Desic- cated Thyroid	Weight, Pounds
10/28/38	-25	615	2.2	0	2.2	1,500	1,100	0.086		179½
10/29/38	-21	640	10.5	8.5	2.3	1,500	1,300	0.083	1 gr	176½
10/30/38						1,500			1 gr	
10/31/38			7.5	6.3	1.3	1,500	2,700	0.113	1 gr	
11/ 1/38	-13	533				1,500	1,700	0.289	1 gr	175
11/ 2/38		535				1,500	800	0.067	1 gr	
11/ 3/38		485	8.2	4.2	4.3	1,500			1 gr	
11/ 4/38	-20	535				1,500	600	0.076	1 gr	172
11/ 5/38	-16	485	11.0	8.4	3.3	1,500	500	0.052	1 gr	171
12/13/38	-9	207	9.0	5.0	4.2				1 gr	169½

* Patient 5—A woman aged 49 had spontaneous myxedema of four years' duration. Classic signs and symptoms of myxedema were observed, with marked arteriosclerosis, essential hypertension of grade II (blood pressure, systolic 180 mm and diastolic 110 mm of mercury) and moderate cardiac enlargement.

Result—Excellent clinical response from an endocrine standpoint was obtained, but six weeks after beginning of treatment with small doses of desiccated thyroid (1 grain [0.065 Gm.] daily) typical angina of effort developed. The patient died at home a few days after the onset of angina, of "an attack of severe pain in the chest and suffocation."

7 Iodine eliminated in sweat and iodine expired through the lungs should be estimated

8 The iodine in the blood should be fractionated into its organic and inorganic components, since organic iodine alone is believed to be physiologically active

All of the foregoing criteria were fulfilled in the present study with the exceptions of the analysis of stools for iodine and the estimation of the iodine content of the food intake and of the iodine lost in sweat and expired in air. However, all patients were on standard hospital diets which were not greatly variable in iodine content. Iodized salt was not

10 Maurer, F. E. Blood Iodine Changes in Menstruation and Pregnancy, *Arch f Gynak* **130** 70-79, 1927. Perkin, H. J., and Brown, B. R. Influence of Thyroid Gland and Ovary on Metabolism of Iodine (Experimental Study in Dog), *Endocrinology* **22** 538-542 (May) 1938. Perkin¹

used The analyses which were not done in this study were not carried out in some of the studies made by other workers¹¹ on the alterations of iodine in the blood in hyperthyroidism Admittedly, this knowledge should be incorporated in a complete metabolic study

Perkin, Brown and Lang^{9b}, Elmer¹², Watson¹³ and Fitz and Hunt¹⁴ have shown by means of iodine tolerance tests that persons with

TABLE 6—Data from Study of the Iodine and Cholesterol Metabolisms in Patient 6

Date	Basal Meta- bolic Rate, Per centage	Plasma Choles- terol, Mg / 100 Cc	Whole Blood, Total Content of Iodine, Micro grams/ 100 Cc	Whole Blood, Con- tent of Organic Iodine, Micro grams/ 100 Cc	Whole Blood, Content of Inor- ganic Iodine, Micro grams/ 100 Cc	Fluid Intake, Cc	Fluid Output, Cc	Iodine Excretion in Urine (24 Hr), Mg	Medi- cation, Thyro- xin Intra- venously	Weight, Pounds
11/ 4/38	—16	277	10.5	8.4	2.2	1,500				75
11/ 5/38	—17	305	9.2	8.4	1.3	1,500	1,650	0.104	0.33 mg	74½
11/ 6/38						1,500	1,900	0.160	0.33 mg	
11/ 7/38	—21	238	10.8	6.3	4.3	1,500	1,550	0.085	0.33 mg	74¼
11/ 8/38						1,500	1,300	0.109	0.33 mg	
11/ 9/38	— 9	243	14.8	6.3	9.3	1,500	1,450	0.173	0.33 mg	73½
11/10/38			13.1	9.6	3.5	1,500	1,300		0.33 mg	
11/11/38						1,500	1,150	0.066	0.33 mg	
11/12/38			24.2	21.1	2.0	1,500	1,250	0.078	0.33 mg	
									Desiccated Thyroid	
12/17/38	+ 2	171	31.0	23.2	7.1		730 (incom- plete)	0.24? (incom- plete)	1 gr	70½
3/25/39	+15	184	6.2	2.1	4.1		350 (incom- plete)	0.756 (incom- plete)	1 gr	75¼

* Patient 6—A girl aged 14 had myxedema of two years' duration. She presented substandard height, slight mental and physical sluggishness, bone age determined by roentgenographic study of the epiphyses of 8 to 9 years, early secondary changes of puberty in the sex organs but no menses and dry skin and coarse straight hair.

Result—Good response to thyroid therapy was obtained, with growth of 1¾ inches (4.45 cm) in height in four and a half months. Results of studies on the iodine content of the blood of this patient possibly were affected by the constant use of iodized salt at home before the patient was admitted to the hospital.

11 Perkin, H. J., Lahey, F. H., and Cattell, R. B. Blood Iodine in Relation to Thyroid Disease. Basic Concept of Relation of Iodine to Thyroid Gland (Iodine Tolerance Test), *New England J Med* **214**: 45-52 (Jan 9) 1936. Perkin, H. J., and Lahey, F. H. Exophthalmic Goiter. Relation Between the Blood Iodine Level and the Duration of Symptoms in Three Hundred and Five Cases, *Arch Int Med* **61**: 875-879 (June) 1938. Perkin, H. J., and Cattell, R. B. Blood Iodine Levels Related to the Recurrence of Hyperthyroidism, *Surg, Gynec & Obst* **68**: 744 (April) 1939.

12 Elmer, A. W. Iodine Tolerance Test for Thyroid Insufficiency, *Endocrinology* **18**: 487-496 (July-Aug) 1934.

13 Watson, E. M. Iodine Tolerance Test for the Investigation of Thyroid Function, *Endocrinology* **20**: 358-362 (May) 1936.

14 Fitz, R., and Hunt, R. S. Experience with Iodine Tolerance Test in "Hypothyroid" Patients, *Tr A Am Physicians* **52**: 24-25, 1937.

hyperthyroidism are "iodophylic", that is, when they are given a specific amount of iodine the iodine in the blood does not rise as high as in normal persons and returns to the basal level more quickly. On the other hand, those with thyroid deficiency are "iodophobic", the blood iodine rises to higher levels than normal after intravenous injection of a given amount of iodine and falls more slowly to the basal level, furthermore, a greater percentage of the iodine administered is recovered in the urine.¹² Perhaps in patients with thyroid deficiency small variations of

TABLE 7—Data from Study of the Iodine and Cholesterol Metabolisms in Patient 7 *

Date	Basal Metabolic Rate, Percentage	Plasma Cholesterol, Mg / 100 Cc	Whole Blood, Total Content of Iodine, Micro grams/ 100 Cc	Whole Blood, Content of Organic Iodine, Micro grams/ 100 Cc	Whole Blood, Content of Inorganic Iodine, Micro grams/ 100 Cc	Fluid Output, † Cc	Iodine Excretion in Urine (24 Hr), Mg	Medication, Desiccated Thyroid	Weight, Pounds
1/11/39	—26	390							141
1/12/39	—17	361	12.3						141½
1/13/39		366	15.7	9.2	6.5	660	0.055		
1/14/39	—41	382	18.0	14.7	3.3	880	0.055		141
1/15/39		372	17.3	12.6	4.7	730	0.540	1 gr	
1/23/39		326						1 gr	135¾
2/10/39		218	10.5	8.4	5.3			1 gr	136½
3/11/39	— 3	235	20.0	7.5	12.5			1 gr	129
4/14/39		250	10.4	5.5	4.2			1 gr	131½
5/31/39		258	4.2	4.2	1.3			1 gr	127

* Patient 7—A woman aged 57 had spontaneous myxedema of fifteen years' duration. Classic signs and symptoms with moderate arteriosclerosis and slight cardiac enlargement were observed.

Result—Good clinical response to relatively small doses of desiccated thyroid was obtained. Results of studies on the content of iodine in the blood of this patient possibly were affected by the application of tincture of iodine to a laceration on the forearm the day before the patient was admitted to the hospital.

† Data on fluid intake are incomplete.

iodine in food intake may cause relatively large fluctuations of the iodine in the blood and in the urine.

Most of the physiologic and metabolic activities are retarded in myxedema. The circulation time is prolonged,¹⁵ the motility and absorptive functions of the gastrointestinal tract are delayed,¹⁶ and finally the activity of all tissue cells is diminished. Presumably, this retardation results from inactivity or atrophy of the acinar cells of the thyroid gland, which are responsible for the conversion of inorganic

15 Macy, J. W., Claiborne, T. S., and Hurxthal, L. M. The Circulation Rate in Relation to Metabolism in Thyroid and Pituitary States (Decholin Method), *J. Clin. Investigation* 15: 37-41 (Jan.) 1936.

16 Althausen, T. L. A Study of the Influence of the Thyroid Gland on the Digestive Tract, *Tr. Am. A. Study Goiter*, 1939, pp. 37-49.

iodine to metabolically active iodine Thus, in patients with myxedema, ingested iodine is slowly and possibly inadequately absorbed, is transported by a relatively stagnant blood stream and is inefficiently utilized These metabolic factors should be borne in mind in the analysis of the results in the study of iodine metabolism

TABLE 8—Data from Study of the Iodine and Cholesterol Metabolisms in Patient 8 *

Date	Basal Meta- bolic Rate, Per- centage	Plasma Choles- terol, Mg / 100 Cc	Whole Blood, Total Content of Iodine, Micro grams/ 100 Cc	Whole Blood, Con- tent of Organic Iodine, Micro grams/ 100 Cc	Whole Blood, Content of Inor- ganic Iodine, Micro grams/ 100 Cc	Fluid Intake, Cc	Fluid Output, Cc	Iodine Excretion in Urine (24 Hr), Mg	Medi- cation, Iodine in Compound Solution of Iodine U S P	Weight, Pounds
1/26/39	-26	388	4.5	3.3	1.3	1,500				162
1/27/39	-38	427	8.6	4.9	3.9	1,500	610	0.038	1.27 mg	161
1/28/39		400				1,500	720	0.124	1.27 mg	
1/29/39		395	9.4	7.5	2.2	1,500	880	0.223	1.27 mg	
1/30/39		395	12.5	8.4	4.5	1,500	490	0.187	1.27 mg	160
1/31/39	-41					1,500	790	0.334	1.27 mg	159½
2/ 1/39		398	36.8	4.2	31.8	1,500	1,200	0.533	1.27 mg	
2/ 2/39	-42		14.4	7.5	6.4	1,500	650	0.302	1.27 mg	158
Desiccated Thyroid										
2/ 3/39		403	8.2	2.9	5.5	1,500	795	0.404	1 gr	
2/ 4/39		400	9.8	4.2	5.4	1,500	655	0.111	1 gr	
2/ 5/39		400	11.2	5.5	5.5	1,500	750	0.128	1 gr	
2/ 6/39	-36	352	8.5	5.0	3.0	1,500			1 gr	157
2/ 7/39		372	9.6	5.0	5.1	1,500	690	0.072	1 gr	
2/ 8/39	-31	342	9.2	6.7	2.2	1,500	815	0.070	1 gr	156
2/ 9/39							275 (incom- plete)	0.029 (incom- plete)	1 gr	
3/ 9/39	-11	162	6.5	2.2	4.3		310 (incom- plete)	0.026 (incom- plete)	1 gr	146½

* Patient 8—A woman aged 36 had spontaneous myxedema of seventeen years' duration. Classic signs and symptoms of myxedema, with moderate arteriosclerosis and cardiac enlargement, were observed.

Result—No clinical response to administration of compound solution of iodine U S P for seven days was obtained. Excellent results followed the administration of desiccated thyroid.

Perkin¹⁷ has shown that in the fractionation of blood iodine by the technic used in this study only organic compounds with a molecular weight of 7,000 and greater are recovered in the organic iodine fraction. Since thyroxin has a molecular weight of 777, it contributes no part to the so-called organic iodine fraction. In the patients who received thyroxin intravenously there was found to be a definite elevation of

17 Perkin, H. J., and Cattell, R. B. The Value of Blood Iodine Estimations in the Diagnosis of Borderline Hyperthyroidism, *Tr. Am. A. Study Goiter*, 1939, pp. 260-276. Perkin¹ Perkin and Hurxthal²

the organic iodine fraction of the blood. Therefore, it may be postulated that the metabolically active substance is not thyroxin but an organic iodine compound with a molecular weight in excess of 7,000. If this is true, thyroxin must be converted into this unknown compound with great facility even in the presence of a deficiency of the thyroid gland. If this is not true, the physiologically active iodine in the blood should be sought in the so-called inorganic iodine fraction.

In the analyses of the behavior of iodine in the cases of myxedema in this study, only observations of trends can be made, since there are exceptions to any conclusion that might be reached. Before the adminis-

TABLE 9—Data from Study of the Iodine and Cholesterol Metabolisms in Patient 9*

Date	Basal Meta- bolic Rate, Per- centage	Plasma Choles- terol, Mg / 100 Cc	Whole Blood, Total Content of Iodine, Micro grams/ 100 Cc	Whole Blood, Con- tent of Organic Iodine, Micro grams/ 100 Cc	Whole Blood, Content of Inor- ganic Iodine, Micro grams/ 100 Cc	Fluid Intake, Cc	Fluid Output, Cc	Iodine Excretion in Urine (24 Hr.), Mg	Medi- cation, Iodine in Potas- sium Iodide	Weight, Pounds
4/12/39		348	6.0							141½
4/14/39	—28		34.6			1,500	530	0.180	1.27 mg	140
4/15/39	—25		11.3	7.1	4.2	1,500			1.27 mg	140
4/17/39	—19	324	10.2	7.0	3.2	1,500			1.27 mg	141
									Desiccated Thyroid	
4/18/39						1,500			1 gr	
4/22/39		262							1 gr	144½
4/29/39		190	7.4	4.2	3.3				1 gr	142
5/6/39		166	5.8						1 gr	141¾
5/20/39		138	6.5	4.2	2.2				1 gr	138

* Patient 9—A woman aged 38 had spontaneous myxedema of seven years' duration. Classic clinical picture of myxedema with amenorrhea of seven years' duration was observed. Result—Good clinical response to treatment with small doses of desiccated thyroid was obtained.

tration of any iodine preparations the levels of total organic iodine and total inorganic iodine in the blood were either low or in the low range of normal (the normal total iodine in the blood being between 5 and 10 micrograms per hundred cubic centimeters of blood and the organic iodine being 65 to 75 per cent of the total iodine). This low level of iodine in the blood in myxedema agrees with the findings of Eisler and Schittenhelm,¹⁸ Curtis and his associates,¹⁹ McCullagh²⁰ and Perkin,²

18 Eisler, B., and Schittenhelm, A. Action of Thyroxin on the Blood Iodine in Myxedema, *Ztschr f d ges exper Med* **68** 487-492, 1929.

19 Curtis, G. M., Davis, C. B., and Phillips, F. J. Significance of Blood Iodine Content of Human Blood, *J. A. M. A.* **101** 901-905 (Sept 16) 1933. Curtis, G. M., Barron, L. E., and Phillips, F. J. Blood Iodine After Total Thyroidectomy in Man, *J. Lab & Clin Med* **20** 813-816 (May) 1935. Curtis⁸

patients 6 and 7 (tables 6 and 7) are exceptions, having elevated iodine levels. It was discovered that patient 7 had applied tincture of iodine liberally to a laceration of the skin one day before the beginning of the study. Patient 6 was found to have been using iodized salt at home before admission to the hospital. Hence, the initial elevation of the iodine in the blood is probably adequately explained in both cases.

It would seem from the results of this study that there is no specificity for the iodine present in thyroid substance to increase the total iodine in the blood or its fractions, that is, any iodine absorbed increased the levels of both organic and inorganic iodine fractions.

TABLE 10—*Relationship Between Intake and Excretion of Fluids and Iodine in Patient 1 (Partly Abstracted from Table 1) **

Date	Fluid Intake, Cc	Fluid Output, Cc	Weight, Pounds	Complete Iodine Excretion in Urine (24 Hr.), Mg	Iodine Content of Medication given, 1 Grain (0.065 Gm.) of Desiccated Thyroid, Mg
10/ 8/38	2,280	1,250	114½	0.026	0.13
10/ 9/38	3,000	2,950		0.062	0.13
10/10/38	2,850	2,750		0.058	0.13
10/11/38	2,550	1,760		0.162	0.13
10/12/38	2,340	3,200	115	0.269	0.13
10/13/38	3,360	3,150		0.202	0.13
10/14/38	3,000	2,800	115	0.282	0.13
10/15/38	2,250	3,100	116	0.507	0.13
10/16/38	2,700	1,420		0.596	0.13
10/17/38	2,160	2,900	111½	0.122	0.13
10/18/38	2,400	2,200	111½	0.202	0.13
Total	28,890	27,480		2.286	1.43

* The total urinary output for the first eleven days of treatment almost equaled the fluid intake. This is a relative diuresis, corroborated by a concomitant loss in weight. The total amount of iodine excreted in the urine surpassed the total amount of iodine administered in medication. During the first three days of treatment the reverse was true. This is possibly an iodine "diuresis."

In the present study, the excretion of iodine in the urine was inconstant and did not appear to bear any definite relationship to the type of iodine administered or to the level of the blood iodine. Nevertheless, there was an increase in the output of iodine in the urine in all instances after treatment.

Table 10, abstracted from table 1, represents the intake and excretion in the urine of both fluids and iodine for the first eleven days of the administration of desiccated thyroid. The total fluid output almost equaled the total fluid intake. This was a relative water diuresis (borne out by concurrent loss in weight). Usually urinary output is only about two-thirds the fluid intake, varying with the amount of fluid lost in perspiration, stools and respiration. This diuretic action of thyroid in myxedema has long been recognized. But it was also noted that the

total iodine excreted surpassed that ingested in medication, despite the fact that in the first three days of study the reverse was true. It would seem from this that there was an iodine excretion following administration of desiccated thyroid greater than that expected in this patient (table 10) even if it were assumed that all the iodine in the desiccated thyroid was excreted in the urine, in addition to the patient's usual iodine output. This "iodine diuresis" following therapy warrants further study with prolonged periods of observation on iodine excretion before and after therapy and accurate knowledge of iodine in food intake. If the aforesaid hypothesis is correct, the phenomenon is analogous to the iodine diuresis in hyperthyroidism, that is, increased active thyroid principle, pathologic or therapeutic, causes increased iodine excretion in the urine. Curtis⁸ has referred to the iodine diuresis in hyperthyroidism as "iodine diabetes."

No absolute correlation was observed between the level of the cholesterol in the blood and the level of the iodine in the blood, either before or after beginning of treatment, but there was a tendency for the level of the organic iodine to be inversely proportional to the level of the plasma cholesterol.

Clinical Observations—In the discussion of the clinical results of this study only a few points need to be emphasized. Excellent symptomatic and objective response from an endocrine standpoint followed the administration of relatively small doses of either desiccated thyroid orally or thyroxin intravenously. One grain (0.065 Gm.) of U. S. P. desiccated thyroid was sufficient to relieve the thyroid insufficiency and maintain adequate thyroid equilibrium in some patients with initial metabolic rates below — 40 per cent. The requirement of only small amounts of thyroid in the successful treatment of many patients with primary myxedema was well demonstrated, although it must be remembered that as a rule patients with hypothyroidism with low metabolic rates require more thyroid medication than those with lesser degrees of hypometabolism.

Thyroxin administered intravenously had no advantages over thyroid given orally except from an experimental standpoint. The iodine compounds (other than thyroid preparations) administered in this study produced no clinical effects on thyroid insufficiency.

A word of caution should be given concerning the treatment of patients of the older age group who are suffering from associated coronary and cerebral arteriosclerosis. The element of danger has been emphasized by many clinicians in the past. Myxedema of long duration results in advanced arteriosclerotic degeneration, which the patient may tolerate fairly well when the metabolic demands are low. Elevation of the metabolism by treatment with thyroid may sometimes be too great a strain for the cardiovascular system, and cerebral and coronary acci-

dents may occur. Patients 2 and 7 well illustrate the hazards of treatment in the presence of degenerative vascular disease, cerebral thrombosis (patient 2) and coronary thrombosis (patient 7) occurred three months and six weeks, respectively, after a daily dose of from 1 to 2 grains (0.065 to 0.13 Gm.) of desiccated thyroid. Bartels and Bell,²⁰ in a recent study, emphasized these dangers.

SUMMARY

The cases of 9 patients with primary myxedema have been studied with particular reference to the behavior of the iodine and cholesterol metabolisms before and after treatment. All patients were hospitalized during the initial part of the study and subsequently examined at frequent intervals in the clinic.

The following observations are in accord with the findings of other investigators: 1. The cholesterol level of the blood was elevated in all cases of thyroid deficiency. 2. After treatment with thyroid preparations was begun the cholesterol level fell in reciprocal relationship to the rise of the basal metabolic rate. 3. The cholesterol level of the blood was a good criterion of the amount of thyroid substance needed after the beginning of treatment. 4. In a case of compensated myxedema without hypometabolism, thyroxin administered intravenously and desiccated thyroid administered orally exerted no effect on the level of cholesterol in the blood.

The specificity of iodine present only in thyroid preparations in lowering the cholesterol level of the blood was demonstrated in 1 case of myxedema, inorganic iodine (in compound solution of iodine U. S. P.) did not alter the level of the cholesterol in the blood. These findings corroborate those of previous investigators.

The difficulties in the analysis of iodine metabolism were discussed.

The levels of the total iodine in the blood and of its organic and inorganic fractions were found to be low or in the low range of normal in 6 of 8 cases of thyroid deficiency. The initial high levels of iodine in 2 cases were explained by ingestion of iodized salt and application of tincture of iodine to the skin, respectively, before the onset of study.

After the administration of small amounts of iodine the level of the iodine in the blood was elevated, but occasionally this elevation persisted for only a few days. No definite difference was noted in the response of the total iodine in the blood or of either of its fractions to the administration of inorganic iodine compounds, iodine in thyroid preparations or organic nonthyroid compounds.

It was demonstrated that the administration of desiccated thyroid to a patient with myxedema produced an iodine "diuresis" analogous to

²⁰ Bartels, E. C., and Bell, G. Myxedema and Coronary Sclerotic Heart Disease, *Tr. Am. A. Study Goiter* 1939, pp. 5-15.

the "diuresis" seen in spontaneous hyperthyroidism. This occurred soon after onset of therapy and could not have been produced by induced hyperthyroidism.

No absolute correlation could be observed between the variations of the level of iodine and the level of cholesterol in the blood in myxedema, but there was a tendency for the level of the organic iodine of the blood to vary inversely with the level of the plasma cholesterol.

Finally, this investigation demonstrated the need for more extensive studies of the metabolism of iodine in myxedema. Longer periods of study of hospitalized patients and more knowledge of the iodine ingested in food and excreted in feces are imperative before definite conclusions may be drawn.

The analyses of blood and of urine were done by Mr. H. J. Perkin's laboratory
918 Medical Arts Building

CONGENITAL BICUSPID AORTIC VALVES

SIMON KOLETSKY, M D

CLEVELAND

Congenital bicuspid aortic valves are of two types, those consisting of two normal cusps and those in which one of the two cusps is subdivided by a ridge of congenital origin into two segments. The first type is evidently due to improper development of the endocardial swellings in the truncus arteriosus that form the rudimentary cusps or possibly to faulty growth of the aortic septum which normally bisects the two lateral endocardial cushions. In the second type there is maldevelopment of a commissure due to arrested growth of the annulus fibrosus and of the projections of the annulus that normally form the commissural cusp margins. The congenital ridge thus represents an abortive and deformed commissure.

A recent survey of records of 3,300 consecutive autopsies at the Institute of Pathology of the University Hospitals of Cleveland revealed 18 cases of congenital bicuspid aortic valve. Nine of these occurred among newborn and other infants and children and 9 among adults. The present report comprises a study of these cases.

INCIDENCE OF CONGENITAL BICUSPID AORTIC VALVES

Within the past five years there have been several reports analyzing from autopsy records the relative incidence of the various congenital anomalies of the heart. From these the data with respect to the incidence of congenital bicuspid aortic valves have been obtained, and they are presented, together with the data of the present study, in table 1. This table gives the total number of consecutive autopsies over a stated period at each institution as well as the number of cases of congenital bicuspid aortic valve.

Because of the variation of the figures and the possibility that the anomaly may be overlooked or incorrectly interpreted, no accurate statistical information is available. The percentage in the figures in table 1 is lower than that in this study (0.54 per cent), but Lewis and Grant¹ found an incidence of 1.4 per cent in 315 autopsies. Adequate examination and correct diagnosis would probably determine an incidence of from 0.5 to 1.0 per cent in the general autopsy population.

From the Institute of Pathology, Western Reserve University and University Hospitals.

¹ Lewis, T., and Grant, R. T. Observations Relating to Subacute Infective Endocarditis, *Heart* **10** 21, 1923.

In the present study a total of 63 cases of 1 or more congenital deformities of the heart was found among 3,300 consecutive autopsies. These deformities were summarized as individual lesions regardless of

TABLE 1—*Incidence of Congenital Bicuspid Aortic Valves in Series of Consecutive Autopsies**

Year of Report	Hospital	Observer	Total Number of Autopsies	Period of Study (Years)	Number of Congenital Bicuspid Aortic Valves
1937	Philadelphia General	Szypulski, J. T. J. Tech Methods 17 119, 1937	7,500	5 (1930-1935)	4
1936	Johns Hopkins	Leech, C. B. J. Tech Methods 15 101, 1936	13,115	34 (1890-1933)	3
1937	University of Pennsylvania	Rannels, H. W., and Propst, J. H. J. Tech Methods 17 113, 1937	4,255	62 (1874-1936)	4
1936	Willard Parker Hospital and Central Neurological Institute	Dolgopol, V. B. J. Tech Methods 16 98, 1936	1,082†	5	0
1936	Massachusetts General	McGinn, S. J. Tech Methods 16 98, 1936	7,500	40 (1895-1935)	10
1938	Children's Memorial, Chicago	Gibson, S., and Clifton, W. M. Am J Dis Child 55 761 (April) 1938	1,950‡	15 (1921-1936)	1
1938	New York	Jacobius, H. L., and Moore, R. A. J. Tech Methods 18 133, 1938	1,600	6 (1931-1937)	4
1940	Institute of Pathology, University Hospitals of Cleveland	Koletsky, S. Present study	3,300	10 (1929-1939)	18

* In addition to the tabulated data it should be said that no instances of congenital bicuspid aortic valve were found in 336 autopsies done at the Buffalo Children's and General hospitals on infants up to 1 year of age, exclusive of stillborn infants (Terplan, K. and Sanes, S. J. Tech Methods 15 86, 1936). Likewise, no instances of this anomaly were present in persons 18 years of age or less among 5,000 persons on whom autopsy was performed at the Mount Sinai Hospital in New York (Gross, L. Arch Path 23 350 [March] 1937).

† The autopsies were limited to children with contagious diseases.

‡ The autopsies were limited to infants and children.

TABLE 2—*Frequency of Congenital Cardiac Anomalies Found Among 3,300 Consecutive Autopsies at the Institute of Pathology, University Hospitals of Cleveland (1929-1939)*

Anomaly	Number of Cases
Bicuspid aortic valve	18
Coarctation of aorta	16
Patent interventricular septum	14
Transposition of the great vessels	13
Patent ductus arteriosus	11
Pulmonary stenosis	7
Bicuspid pulmonary valve	7
Supernumerary pulmonary cusp	5
Bicuspid tricuspid valve	5
Tricuspid mitral valve	2

whether they occurred in combination with other anomalies or whether they were of primary or secondary importance, and then the most common lesions were tabulated in the order of frequency (table 2). Instances of anatomically patent foramen ovale in patients of all ages

and of patent ductus arteriosus in infants 2 months or less of age were excluded² The congenital bicuspid aortic valve, occurring in 18 cases, was the most common single cardiac anomaly, followed by coarctation of the aorta in 16 and a patent interventricular septum in 14 Malformations were more frequent in the aortic valve than in any other valve The pulmonary valve was bicuspid in 6 cases and had a supernumerary cusp in 5, while there were 5 cases of a two-cusped right atrioventricular valve and 2 of a tricuspid left atrioventricular valve

REPORT OF CASES

In the present study the cases have been divided into two groups Group I consists of 9 cases in which the patients were newborn, infants and children, while group II comprises 9 cases in which the condition occurred in adults

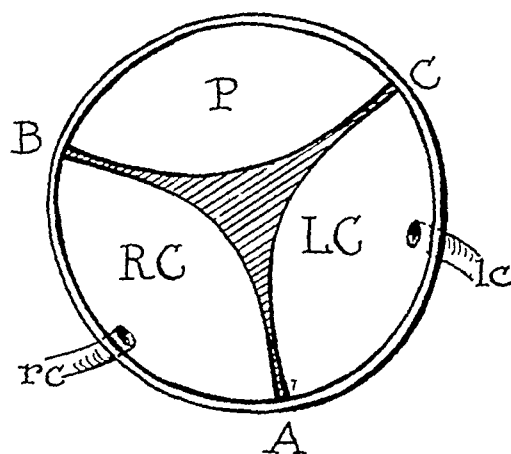


Fig 1—Diagram illustrating the nomenclature of the aortic valve *LC*, left coronary cusp, *RC*, right coronary cusp, and *P*, posterior, or noncoronary, cusp, *A*, left coronary-right coronary commissure, *B*, right coronary-posterior commissure, *C*, left coronary-posterior commissure, *lc*, left coronary artery, *rc*, right coronary artery

For convenience, the aortic cusps will be designated according to the situation of the ostiums of the coronary arteries as the left coronary (*LC*), the right coronary (*RC*) and the noncoronary, or posterior (*P*), cusps The left coronary-right coronary commissure will be referred to as commissure *A*, the right coronary-posterior commissure as commissure *B* and the left coronary-posterior commissure as commissure *C*, as explained in the legend to figure 1

² Anatomically patent foramen ovale was observed in approximately 15 per cent of all autopsies Unless unusually large, a patent ductus arteriosus was considered abnormal only after the second postnatal month

GROUP I

CASE 1—A $2\frac{1}{2}$ year old white boy died of severe rickets and acute bronchiolitis

The heart weighed 55 Gm (expected weight 68 Gm) and was normal except for a bicuspid aortic valve (fig 2) This consisted of a conjoined left and right coronary cusp, 1.4 cm in length, and a noncoronary cusp, 1.2 cm long Commissure A was replaced by a slightly elevated ridge of firm tissue, 8 by 2 by 1.5 mm, which divided the conjoined cusp unequally into a small left coronary and a larger right coronary segment The ridge extended from the upper level of the sinus of Valsalva to within 1 mm of the floor of the sinus, where it divided into a right and a left lateral subsidiary branch These pursued a short oblique course toward the free margin of the conjoined cusp Commissures B and C were normal Both aortic cusps showed slight fleshy thickening

No microscopic sections of the aortic valve were made

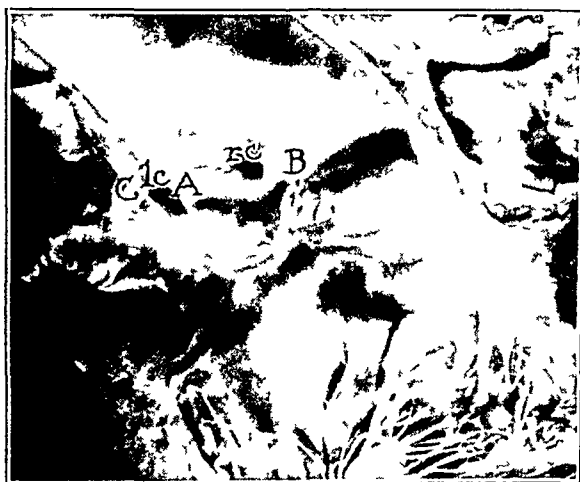


Fig 2 (case 1)—Bicuspid aortic valve in a $2\frac{1}{2}$ year old white boy There is a congenital ridge at commissure A which divides the conjoined cusp of the aortic valve unequally into a small left coronary and a larger right coronary segment In this figure and in the accompanying figures, *A* represents the left coronary-right coronary commissure, *B* the right coronary-posterior commissure and *C* the left coronary-posterior commissure, while *lc* and *rc* indicate the ostia of the left and the right coronary artery, respectively

CASE 2—A 1 day old white boy died of acute purulent meningitis complicating meningomyelocele

The heart weighed 35 Gm (expected weight 23 Gm) The aortic valve measured 2.5 cm in circumference and consisted of two well formed cusps, equal in length These were a right and a left coronary cusp, each showing in its sinus of Valsalva the ostium of the corresponding coronary artery There was no vestige of a third cusp or of a congenital ridge Both cusps showed slight nodular thickening of the free margins

No microscopic sections of the aortic valve were made

3 Expected weights of the hearts in this group of cases were obtained from Roessle and Roulet (*Mass und Zahl in der Pathologie*, in Aschoff, L , Elias, H , Eppinger, H , Sternberg, C , and Wenckebach, K F *Pathologie und Klinik in Einzeldarstellungen*, Berlin, Julius Springer, 1932, vol 5)

CASE 3—A white boy 9 weeks of age had clinical diagnoses of bronchopneumonia and idiopathic hypertrophy of the heart

The heart weighed 77 Gm (expected weight 25 Gm) and was the seat of diffuse fatty degeneration. The aortic valve consisted of two cusps, a left coronary and a combined right coronary and posterior cusp. The latter was approximately twice the size of the former and was bisected evenly at commissure B by a long low ridge with sharply defined, parallel lateral borders and a smooth, round outer surface. There was marked retraction of the ventricular aspect of the conjoined cusp opposite the ridge. Commissures A and C were normal.

Microscopic sections of the aortic valve showed no vascularization and no inflammation. There was marked irregular fibrous thickening of the cusps, especially of the fibrosa layer. The congenital ridge was not examined histologically.

CASE 4—The child was a newborn full term white boy.

The heart weighed 40 Gm (expected weight 23 Gm) and showed numerous congenital anomalies (table 3). The aortic valve was composed of two thin and delicate cusps, equal in length. One was a conjoined right and left coronary cusp, subdivided evenly at commissure A by a narrow longitudinal ridge, 5 by 0.8 by 0.8

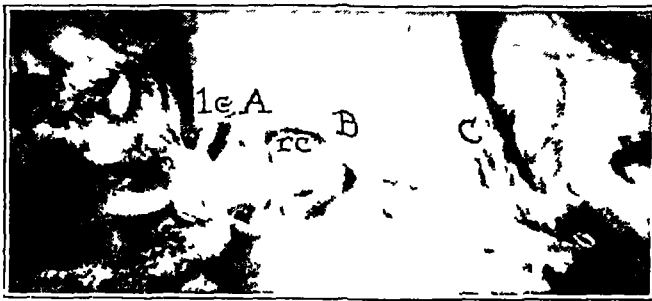


Fig 3 (case 4)—The anomaly in a newborn white boy. The combined left and right coronary cusps of the aortic valve are bisected by a congenital ridge at commissure A. Note the small subsidiary ridges at the termination of the main ridge.

mm (fig 3). The ridge projected slightly from the aortic wall of the sinus of Valsalva and extended from the upper level of the sinus to its floor, where it terminated by dividing into several small branches. Its outer surface was smooth and rounded and showed no fissure or raphe. There was no retraction of the ventricular surface of the conjoined cusp.

Serial transverse microscopic sections of the congenital ridge revealed no vascularization or inflammatory change⁴. The first 2.5 mm showed dense elastic fibers continuous with those of the aortic media. Superficially and at the sides

4 Microscopic sections of the congenital ridges were studied with the hematoxylin and eosin stain, with the Verhoeff and the Weigert technic for elastic tissue and with the combined Verhoeff and Van Gieson methods for elastic and connective tissue. The descriptions in the text are based largely on the stains for elastic tissue, since they showed clearly the distribution of the aortic media in the ridge and the relation of the media to the annulus fibrosus.

and base of the ridge the elastic laminae were parallel, while in the midportion they showed an irregular whorling pattern. Halfway down the ridge the elastica in the central portion began to be replaced by collagenous connective tissue of the annulus fibrosus. As the elastic fibers thinned out they maintained a position superficial to the annulus, and finally only a single subendocardial band of elastica could be traced across the ridge. The overlapping junction of the media and the annulus fibrosus occupied a distance of 1 mm.

The subsidiary ridges consisted of a superficial layer of dense collagenous connective tissue, which was moderately cellular, and a basal layer of loose, myxomatous-like tissue.

CASE 5—The child was a newborn full term white girl.

The heart weighed 26 Gm (expected weight 21 Gm) and was normal except for a congenital bicuspid aortic valve. This consisted of a combined right coronary and posterior cusp, 1.5 cm in length, and a smaller left coronary cusp, 0.9 cm long (fig 4a). The conjoined cusp was evenly subdivided at commissure B by a congenital ridge and showed marked retraction on its ventricular aspect opposite the ridge. At the apex of the retracted area was a hemangiomatic nodule, 2 mm in diameter. Each coronary ostium was situated as usual at the upper border of the sinus of Valsalva of its corresponding cusp. Commissures A and C were normal.

The congenital ridge measured 3 by 1 by 1 mm and consisted of a slightly elevated longitudinal fold of aorta with parallel lateral borders and a smooth, symmetrically rounded outer surface. At its termination in the floor of the sinus of Valsalva there were lateral subsidiary branches as well as a small fleshy fold of connective tissue, which continued directly forward almost to the free margin of the cusp. The triangular portion of free cusp bounded by the lateral ramus and the free margin showed slight thickening, while the rest of both cusps was thin and delicate.

Longitudinal microscopic sections of the congenital ridge showed that it was composed of aortic media, which extended the entire length of the ridge down to the attachment of the cusp (fig 4b). At the base of the ridge the annulus fibrosus sent a tongue-shaped projection of tissue upward for a distance of 0.8 mm, which was overlapped both superficially and deeply by the elastica. The deep elastic fibers extended to a lower level than the superficial elastica.

CASE 6—An 8 year old white boy died of extensive subarachnoid hemorrhage, due to a ruptured congenital aneurysm of the circle of Willis.

The heart weighed 175 Gm (expected weight 113 Gm). There was hypertrophy of both ventricles, especially of the left, but otherwise the myocardium was not remarkable. The aortic valve was composed of two cusps, one of which represented a conjoined left and right coronary cusp. This was exactly bisected by a narrow ridge of firm tissue extending from the upper limit of the sinus of Valsalva to the free margin of the cusp. The coronary ostia were placed to either side of the ridge in their usual positions. Commissures B and C showed no abnormality. There was slight thickening of the free margins of the cusps.

No microscopic sections of the aortic valve were made.

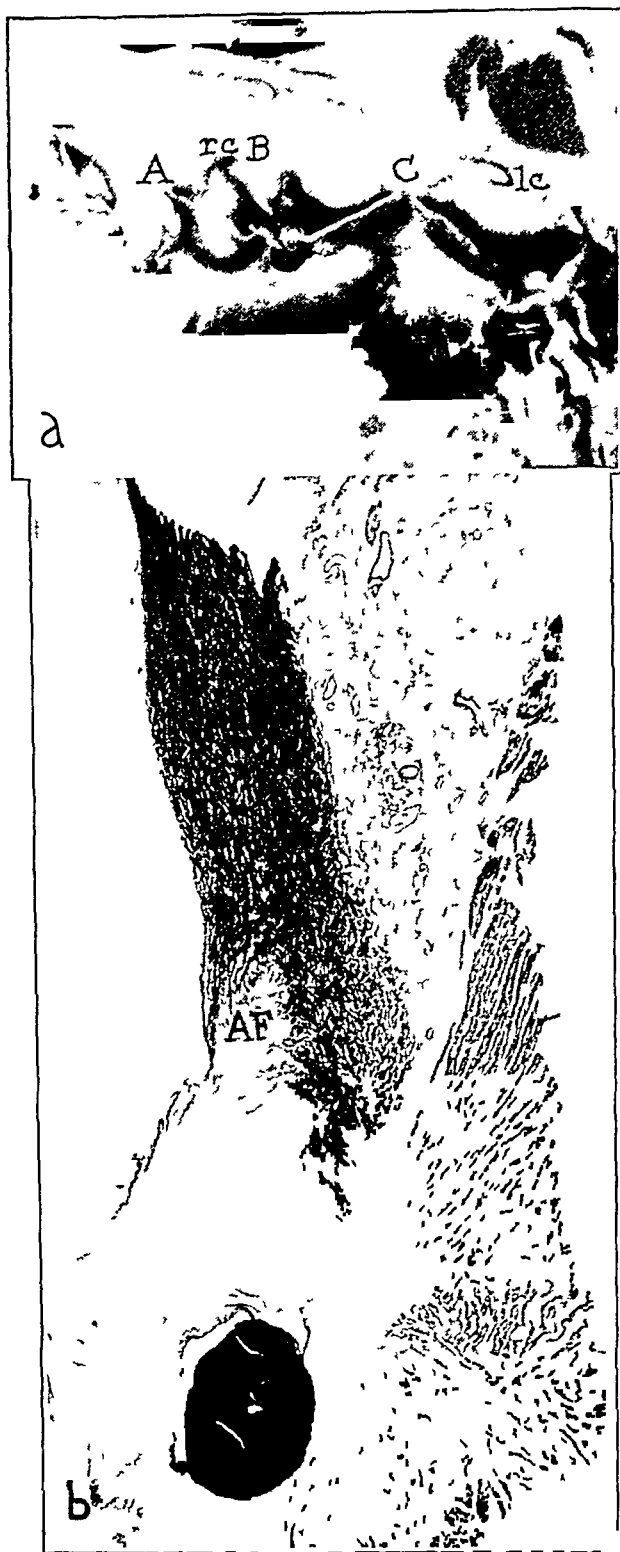


Fig 4 (case 5) —Congenital bicuspid aortic valve in a newborn white girl
 (a) Commissure B shows a congenital ridge. The lateral borders of this ridge appears to converge because of the angle at which the photograph was taken, but actually they were parallel. (b) Longitudinal section of the congenital ridge (Verhoeff elastic stain, $\times 15$). The ridge shows dense elastic laminae derived from the aortic media. At its base the annulus fibrosus (AF) is overlapped both superficially and deeply by elastica, and the deep elastic fibers extend to a lower level than the superficial. There is a hemangiomatous nodule at the free margin of the cusp.

CASE 7—A white girl 9 months of age died of bronchopneumonia

The heart weighed 665 Gm (expected weight 36 Gm) The aortic valve consisted of a conjoined left and right coronary cusp, 1.5 cm in length, and a noncoronary cusp, 1 cm long (fig 5*a*) Commissure A was replaced by a congenital ridge which divided the fused cusp unevenly into a left coronary portion, 0.6 cm long, and a larger right coronary segment, 0.9 cm in length There was slight retraction on the ventricular aspect of the conjoined cusp opposite the ridge

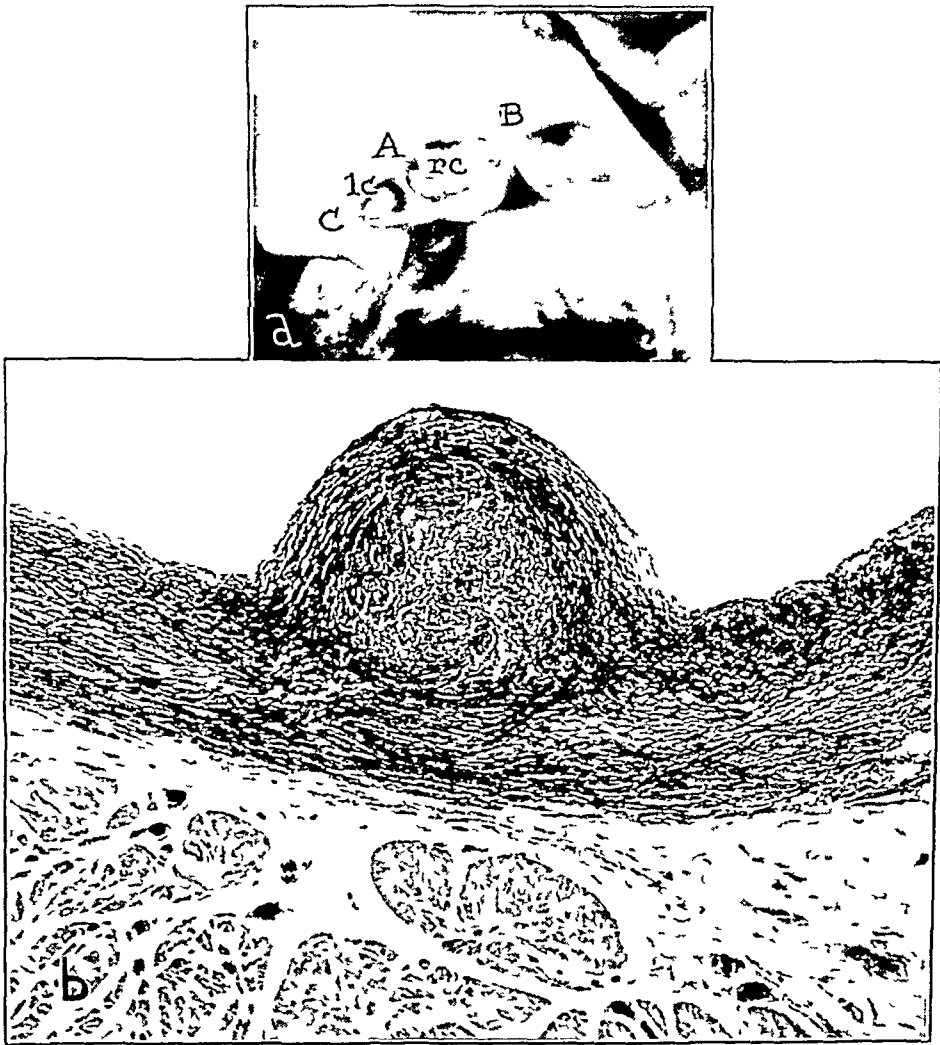


Fig 5 (case 7) —The congenital anomaly in a 9 month old white girl (a) Commissure A of the aortic valve is replaced by a congenital ridge which divides the conjoined cusp into a left coronary and a larger right coronary segment In this instance the lateral borders of the ridge are converging rather than parallel (b) Transverse microscopic section of the proximal portion of the congenital ridge (Verhoeff elastic stain, $\times 25$) The ridge shows bundles of elastic tissue derived from the aortic media, and in the center these have a whorled pattern The anuulus fibrosus is not seen at this level

The lateral borders of the ridge were converging in its proximal half and parallel in the distal half, which consisted of a narrow fold of fibrous tissue Both cusps were thin and delicate Commissures B and C were normal

Serial transverse microscopic sections of the congenital ridge revealed a symmetric architecture with no vascularization or inflammatory change. The first millimeter showed numerous elastic lamellae derived from the aortic media, and in the central portion of the ridge these had a whorled pattern (fig 5*b*). At the beginning of the narrow segment of the ridge the elastica began to be replaced by connective tissue of the annulus fibrosus. The junction of media and annulus occupied a distance of 0.5 mm, and the media overlapped the annulus both superficially and deeply, with the superficial elastica terminating at a lower level.

CASE 8—A white girl 20 months of age died of tuberculous meningitis.

The heart weighed 80 Gm (expected weight 54 Gm). The aortic valve consisted of two well formed cusps of equal size, each 1.5 cm in length (fig 6). One of these the right coronary cusp, was situated to the right and slightly anteriorly and the other the left coronary cusp to the left and slightly posteriorly. There was no suggestion of a third cusp. The coronary ostia were situated behind their respective cusps and the right coronary ostium was displaced, being



Fig 6 (case 8)—The congenital anomaly in a white girl 20 months of age. The aortic valve consists of two well formed cusps instead of three. Both cusps are thick, fleshy and opaque.

only 1 mm from the anterior commissure. Both cusps were thick, fleshy and opaque. The commissures were rendered prominent by the presence of elevated intimal hyaline plaques of the aorta. The anterior leaflet of the mitral valve revealed numerous irregular, flat, yellow atheromatous plaques, from 1 to 5 mm in diameter, on its aortic aspect.

Longitudinal microscopic sections through the midportion of the right coronary cusp showed slight thickening of the fibrosa layer. Otherwise there was no significant change.

CASE 9—A white boy 17 days of age died of bronchopneumonia.

The heart weighed 40 Gm (expected weight 24 Gm). The aortic valve was composed of two slightly thickened and opaque cusps (fig 7).⁵ One of these was 1.2 cm long and represented a fused right and left coronary cusp, while the other

⁵ Congenital ridges were present at both commissures A and B. For simplification the combined left and right coronary cusp will be considered the conjoined cusp.

was a noncoronary cusp and measured 0.8 cm in length. Each coronary ostium was situated as usual in the sinus of Valsalva of its corresponding cusp.

Commissures A and B were replaced by congenital ridges, which were similar in appearance and measured 6 by 1 by 0.5 mm. Each projected only slightly from the aortic wall of the sinus of Valsalva and extended from a point 1 mm above the sinus to the attachment of the cusp. The outer surface of ridge A was smooth in its proximal half, while the distal half was bisected by a longitudinal fissure. The ridge at commissure B showed a similar fissure terminally for a distance of 1 mm. There were no subsidiary ridges. The ventricular aspects of the cusps showed slight retraction opposite each congenital ridge. Commissure C was normal.

Serial transverse microscopic sections of the two ridges were similar. They showed dense elastic lamellae continuous with the aortic media, and these passed uninterruptedly across the ridge. The elastica in ridge A began to show replacement by the annulus fibrosus midway in its course, and the replacement was complete 1.5 mm further down. In ridge B the elastica was continued far down the ridge, and the junction between elastica and annulus fibrosus did not begin until just before the commencement of the fissure. The elastic tissue was then completely replaced within a distance of 0.5 mm. In both ridges the termination



Fig 7 (case 9)—The congenital anomaly in a white boy 17 days of age. Congenital ridges are situated at both commissures A and B. These project uniformly and only slightly from the aortic wall of the sinus of Valsalva and have parallel lateral borders. The lower portion of each ridge is bisected by a longitudinal fissure.

of the elastica was superficial to the annulus. Neither ridge showed any vascularization or inflammatory change.

GROUP II

CASE 10—A 47 year old Negro man died in uremia, due to congenital polycystic kidneys.

The heart, the seat of hypertrophy and dilatation, weighed 690 Gm. There was no abnormality of the mitral, tricuspid or pulmonary valves. The aortic valve consisted of two thickened and opaque cusps. One was a combined right and left coronary cusp, 5 cm in length, and was placed to the right and anteriorly. The other (the noncoronary cusp) was situated to the left and posteriorly and was 3 cm long. Both coronary ostia were found in the sinus of Valsalva corresponding to the larger anterior cusp. There was no suggestion of a third cusp or of a congenital ridge.

Microscopic sections showed marked fibrosis and hyalinization of the cusps at the base and near the free margins. There was no vascularization or inflammatory change. Sections of the mitral and tricuspid valves revealed no abnormality.

CASE 11—A 39 year old white housewife had a pathologic diagnosis of rheumatic heart disease with mitral, tricuspid and aortic valvulitis and mitral and tricuspid stenosis

The heart weighed 270 Gm. The aortic valve was composed of two cusps of equal size, each 3.8 cm in length. These were the right and the left coronary cusps, and in their sinuses of Valsalva were the ostiums of the right and the left coronary artery, respectively. No congenital ridge was present. Both cusps were moderately thickened throughout and showed a few calcific nodules both at the base and at the free margin. There were no adhesions at the commissures.

Microscopically the cusps showed marked fibrous thickening and hyalinization, especially in the vicinity of the commissures, but there was no vascularization or cellular exudate. The mitral and tricuspid leaflets also showed fibrous thickening, and in the mitral leaflet there were small, thick-walled blood vessels extending from the base almost to the free margin.

CASE 12—A 26 year old white man died of bilateral bronchopneumonia and multiple abscesses of the lung.

The heart weighed 275 Gm, and the only abnormality was a congenital bicuspid aortic valve. This was composed of two well formed but slightly thickened cusps, each measuring 3 cm in length. One was placed to the right and anteriorly and contained the right coronary ostium in its sinus of Valsalva, while the other was situated to the left and posteriorly and showed the left coronary ostium in its sinus. No congenital ridge was present. Both the circumference of the ring of the valve and that of its free margin measured 6 cm. The commissures showed no significant change.

Microscopic sections revealed slight fibrous thickening and hyalinization of the annulus fibrosus and of the fibrosa layer of the cusps. No vascularization or inflammatory exudate was present.

CASE 13—A 52 year old white man had clinical diagnoses of aortic stenosis, probably rheumatic in origin, and cardiac failure.

The heart, the seat of hypertrophy and dilatation, weighed 550 Gm. The orifice of the aortic valve was slitlike, measuring 2 cm in length and only 1.5 mm in width. The valve consisted of two cusps of equal length, each measuring 2.5 cm. One was situated to the right and anteriorly and the other to the left and posteriorly. Both were markedly thickened and calcified and were rigid and immobile. Areas of atheromatous ulceration were present on the ventricular and the aortic aspect, and the sinuses of Valsalva were partly filled with large nodular calcific excrescences.

There was a congenital ridge at the site of commissure A (fig 8a) which subdivided the conjoined right and left coronary cusp into two equal parts. The ridge resembled a hemicylindric elevation of aorta which projected slightly and uniformly into the sinus of Valsalva. Its lateral borders were parallel, and the outer surface was smooth and rounded with no fissure or raphe. It measured 4 by 1 by 1 mm and extended from a point 3 mm below the upper limit of the sinus of Valsalva to the floor of the sinus, where it was crossed by an S-shaped, pale gray, calcified fold of tissue. Beyond this, the main ridge was continued to the free margin of the cusp in the form of a smaller ridge, the surface of which was studded with calcified nodules. The ventricular aspect of the combined cusp showed no retraction.

Serial transverse microscopic sections were made of the congenital ridge. The proximal half showed considerable elastic tissue arranged in parallel lamellae in all but the central portion, where there were whorling and irregularity (fig 8b).

Beneath the elastica, which extended down to the attachment of the cusp before disappearing, was the annulus fibrosus, occupying the lower half of the ridge. The annulus was densely hyalinized, as was the small ridge on the aortic aspect of the conjoined cusp, which showed numerous calcific nodules. Throughout the ridge there was no vascularity or cellular exudate.

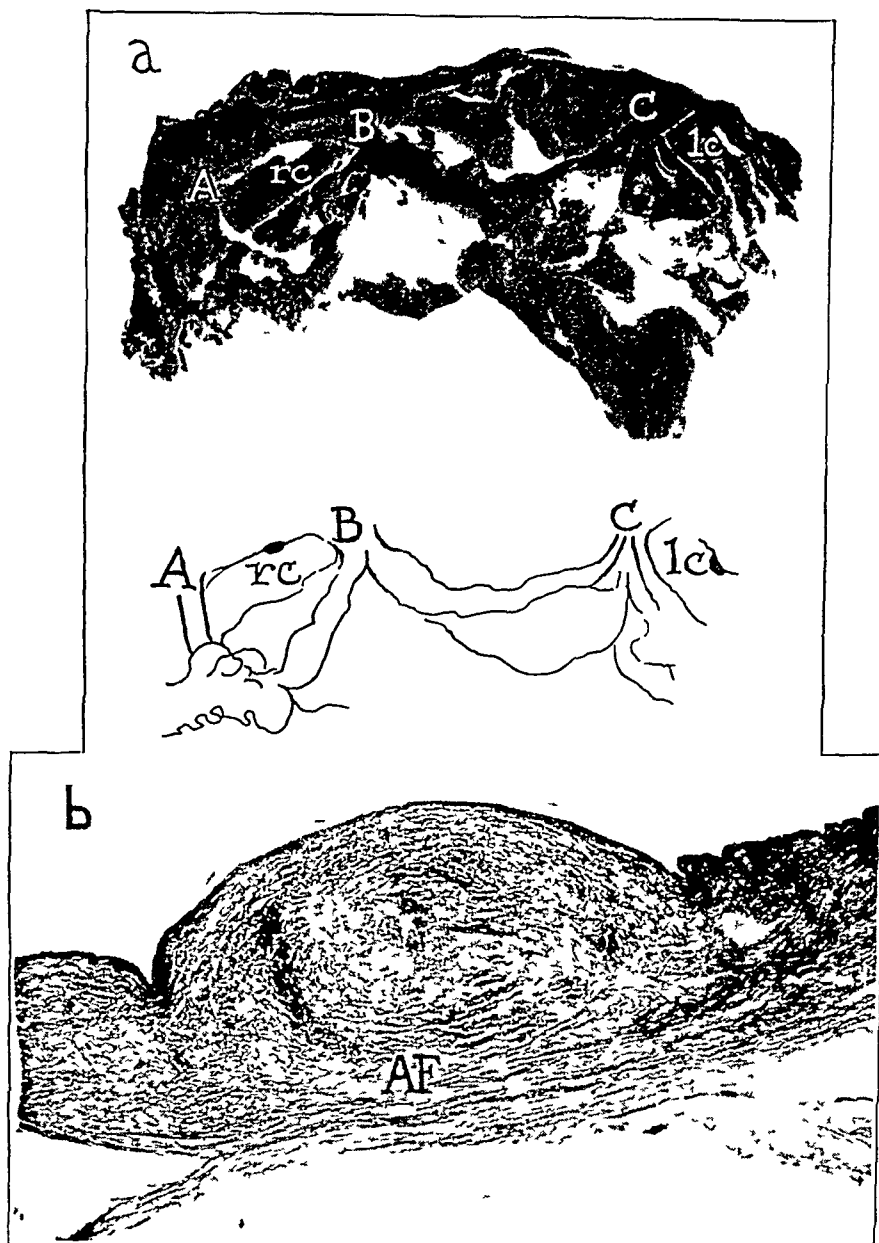


Fig 8 (case 13) —(a) Extensive calcific sclerosis of the aortic valve in a 52 year old white man. A typical congenital ridge is shown in lateral view at commissure A. Note the uniform projection into the sinus of Valsalva throughout its course, which is parallel with the long axis of the aorta. The ridge is not involved by the calcific disease. (b) Transverse section of the proximal portion of the congenital ridge (Verhoeff elastic stain, $\times 20$). Elastic laminae pass uninterruptedly across the ridge in parallel fashion except in the center, where there are whorling and irregularity. At the base of the ridge the elastica shows beginning replacement by the connective tissue of the annulus fibrosus (AF).

Longitudinal sections of the cusps showed marked fibrosis and hyalinization of all layers, especially the fibrosa, with numerous nodules of calcium and several areas of bone formation, one of which revealed a fatty marrow. The ring of the valve was vascularized and showed lymphocytic exudate. In the free portion near the spicules of bone there were numerous capillaries and arterioles together with infiltration of lymphocytes, plasma cells and monocytes.

Numerous sections of various portions of the heart, including the mitral, tricuspid and pulmonary valves, showed no evidence of chronic or healed rheumatic disease.

CASE 14—A 58 year old white man died of confluent bronchopneumonia.

The heart weighed 300 Gm, and the only significant lesion was in the aortic valve. This was composed of two cusps. The larger, which represented a combined right coronary and noncoronary cusp, was situated to the right and showed the orifice of the right coronary artery in its sinus of Valsalva. The smaller cusp was placed to the left, and in its sinus was the ostium of the left coronary artery. Both cusps were thick and opaque, and their aortic aspects were studded with hard calcified nodules, which extended from the base to the free margin.

Microscopic sections showed considerable thickening of the cusps in all layers by mature connective tissue, portions of which were hyalinized and contained areas of calcification. Vascularization was limited to the ring of the valve, and there was no leukocytic exudate. Sections of the mitral valve showed no abnormality.

CASE 15—A 43 year old white man died of peritonitis following rupture of the appendix. Clinical diagnoses of congenital heart disease and gout were also made.

The heart, the seat of hypertrophy and dilatation, weighed 700 Gm. There were several congenital anomalies (table 3, group II). The aortic valve consisted of two cusps instead of three. One was situated to the right and anteriorly and was slightly larger than the other, which was placed to the left and posteriorly. The former presented the ostium of the right coronary artery in its sinus of Valsalva, while the latter showed the opening of the left coronary vessel. There were slight adhesions at both the anterior and the posterior commissure. Both cusps were irregularly thickened and shortened, and small calcified nodules were deposited along the base on their aortic aspects. There was slight calcification of the rings of the mitral, pulmonary and tricuspid valves.

No microscopic sections of the valves were made.

CASE 16—A 38 year old white man had clinical and pathologic diagnoses of acute pancreatic necrosis and bronchopneumonia. Physical examination did not reveal any abnormality of the heart.

The heart weighed 450 Gm, the enlargement being due chiefly to hypertrophy of the left ventricle. The mitral, tricuspid and pulmonary valves showed no abnormality. The aortic valve consisted of two cusps, which were thick, fleshy and opaque (fig 9a). One was a conjoined right coronary and posterior cusp, 4.5 cm in length, while the other was a left coronary cusp, 2.5 cm long. The conjoined cusp was subdivided evenly by a congenital ridge situated at commissure B and measuring 12 by 2 by 2 mm. The outer surface of the ridge was smooth and rounded except at its termination, where it was slightly irregular owing to the presence of small calcific nodules. The outer free portion of conjoined cusp adjacent to the ridge showed fibrous thickening and calcification.

Longitudinal microscopic sections of the entire congenital ridge showed dense bundles of parallel elastic laminae continuous with those of the aortic media and

extending down practically to the attachment of the cusp, a distance of 1 cm (fig 9 *b*) The elastica began to be replaced by the annulus fibrosus about 5 mm from the beginning of the ridge, and in its terminal portion it was superficial to



Fig 9 (case 16) —Congenital bicuspid aortic valve in a white man aged 38 (a) The right coronary and the posterior aortic cusp form a conjoined cusp with a congenital ridge at commissure B There are fibrous thickening and calcification at the termination of the ridge and in the adjacent free portion of the cusp (b) Longitudinal section of the congenital ridge (Verhoeff elastic stain, $\times 25$) The ridge shows dense bundles of elastic tissue extending almost to the insertion of the cusp At its termination the elastica is superficial to the annulus fibrosus (AF)

the annulus. There was fibrous thickening of the annulus, and its distal segment showed several calcified nodules. There were also fibrosis and hyalinization of the cusps, but no vascularization or inflammation was found. The ridge showed no vascularity or exudate.

Numerous sections of the heart, including the mitral, pulmonary and tricuspid valves, showed no evidence of rheumatic disease.

CASE 17—A white man aged 39 had a clinical diagnosis of rheumatic heart disease with aortic stenosis and mitral insufficiency. There was a history of one attack of acute rheumatic fever at the age of 10 years.

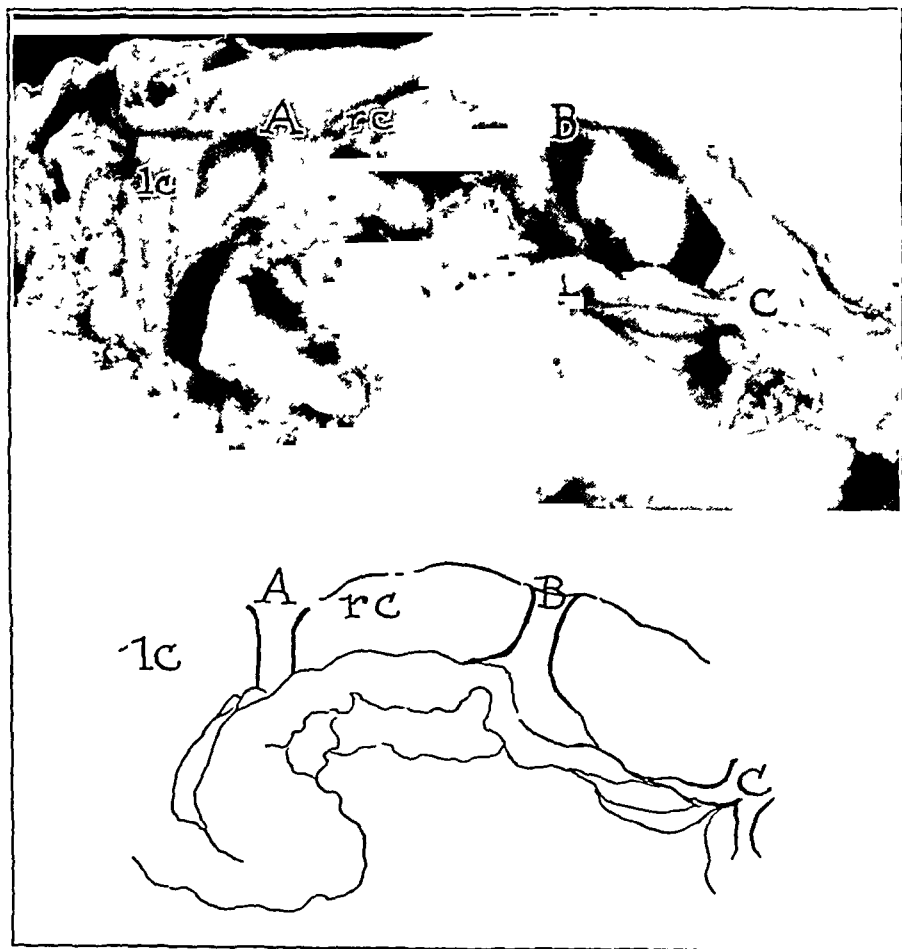


Fig. 10 (case 17) —Extensive calcific sclerosis of the aortic valve in a white man aged 39. There are congenital ridges at commissures A and B, with distinct triangular retractions opposite them on the ventricular aspect of the cusps.

The heart weighed 550 Gm, and the enlargement involved essentially the left ventricle. The mitral, tricuspid and pulmonary valves showed no abnormality. The aortic valve was composed of two thick and calcified cusps, which were rigid and immobile (fig. 10). One was situated to the right and slightly anteriorly and measured 3.5 cm. in length, while the other was placed to the left and posteriorly and was 2.5 cm. long⁶. There were areas of atheromatous ulceration on both the

⁶ The combined left coronary and right coronary cusps will be considered as the conjoined cusp. In this case and in case 9 the aortic valve was actually monocuspid.

ventricular and the aortic aspects near the free margin. The orifice of the valve was a narrow slit, 2 cm long and only 3 mm in width.

At commissure A there was an elongated ridge of firm tissue, 6 by 2 by 1 mm. This extended down from the upper level of the sinus of Valsalva, the lateral portions of the adjacent coronary cusps inserting at its termination. There was a distinct triangular depression opposite the ridge on the ventricular aspect of the conjoined cusp. The coronary ostiums occupied their usual positions to either side of the ridge. Commissure B was the site of a similar ridge, which projected only 0.5 mm into the sinus of Valsalva throughout its length. Its outer surface was smooth and symmetrically rounded and showed no fissure. The ridge bisected the combined right coronary and posterior cusp evenly, the ventricular aspect of the cusp showing a distinct triangular retraction. Commissure C was normal.

Serial transverse microscopic sections of the ridges were similar. Bundles of elastic tissue were elevated into the ridge from the aortic media and were parallel except in the central portion, where there was distinct whorling. This was more marked in ridge B. In each ridge the media descended to the attachment of the cusps. In ridge A the annulus fibrosus was only 1 mm in extent and was situated superficially in relation to the elastic tissue. In commissure B the annulus sent a projection of fibrous tissue 2.5 mm long upward from the base of the ridge, and this was overlapped by superficial and deep extensions of the elastic media, both of which terminated at the attachment of the cusps.

Sections of the aortic cusps revealed marked fibrosis, hyalinization and calcification, especially of the ventricularis and spongiosa layers, together with vascularization and lymphocytic exudate. The ring of the valve was also vascularized and showed infiltration of lymphocytes. Sections of the mitral valve revealed no inflammation, but there were several thick-walled small arteries and arterioles in the auricularis and spongiosa layers. The tricuspid and pulmonary valves showed no abnormality.

CASE 18—The clinical data of this case are not available.

The heart, the seat of hypertrophy and dilatation, weighed 500 Gm. The mitral, tricuspid and pulmonary valves revealed no significant gross change. The aortic valve consisted of two cusps, 3.5 and 3 cm in length, respectively (fig 11). The larger was a combined left and right coronary cusp, which was evenly bisected by a congenital ridge, and the smaller was the noncoronary cusp. The coronary ostiums occupied their usual positions in the sinuses of Valsalva of the conjoined cusp. Commissure A was replaced by a slightly elevated hemicylindric ridge with parallel lateral borders, measuring 12 by 1.5 by 1 mm. For the first 8 mm its outer surface was smooth and rounded and showed no fissure, then for the remaining 4 mm there was a median longitudinal fissure. Lateral rami arose from the ridge terminally, while the main ridge was continued halfway to the free margin of the cusp as a small, slightly elevated fold, 5 mm in length. There were numerous friable, grayish red vegetations on the aortic and ventricular aspects of both cusps near their free margins, and these were firmly attached to the underlying endocardium. The congenital ridge was not involved by the inflammatory process. Commissures B and C were normal.

Longitudinal microscopic sections of the congenital ridge revealed parallel elastic lamellae in the first 7 mm. For the next 5 mm the elastica was in contact with the annulus fibrosus, which it overlapped with both superficial and deep projections. These terminated at the same level. No portion of the ridge showed vascularization or cellular exudate.

Sections of the aortic cusps showed numerous bacterial vegetations near the free margin, with organization at their base. There were also diffuse leukocytic exudate and vascularization, especially of the ventricularis layer. Sections of

the mitral valve showed areas of lymphocytic and polymorphonuclear exudate as well as numerous arterioles and capillaries in the auricularis layer near the free margin

SUMMARY OF EIGHTEEN CASES OF CONGENITAL BICUSPID AORTIC VALVE

The data with regard to age, sex and color, together with the clinical diagnoses and the associated cardiac and extracardiac anomalies, are recorded in table 3

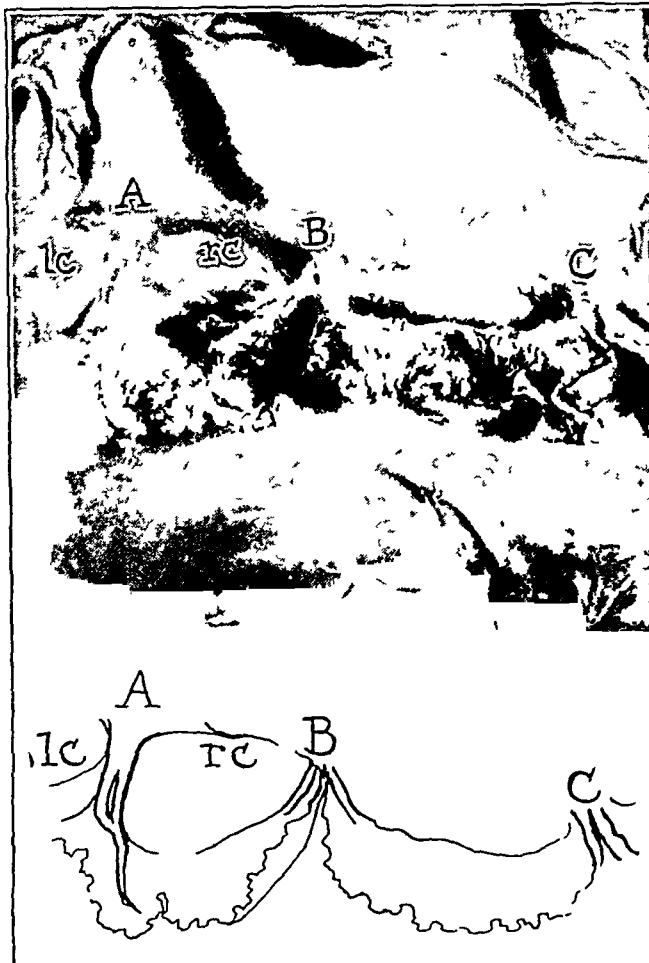


Fig 11 (case 18) —Subacute bacterial endocarditis of the aortic valve The congenital ridge at commissure A is typical except for the longitudinal fissure in its lower portion The ridge is not involved by the inflammatory process

1 *Age, Sex and Color* —In 7 of the 9 cases in group I the condition occurred in infants 20 months of age, or less, and 3 of these were newborn In 1 case the patient was a 2½ year old boy and in 1 an 8 year old boy who died of cerebral hemorrhage due to a ruptured congenital aneurysm of the circle of Willis Among the adults the youngest was 26 and the oldest 58 Seven of the patients were over 35 years of age

TABLE 3—*Congenital Bicuspid Aortic Valves*

Case	Age, Sex, Color	Clinical Diagnosis	Other Cardiac Anomalies	Extracardiac Anomalies
Group I Newborn and Other Infants and Children (9 Cases)				
1	2½ years Male White	Severe rickets with osteoporosis, cirrhosis of liver, secondary anemia	None	None
2	1 day Male White	Meningocele, acute suppurative meningitis	Bicuspid pulmonary valve	Meningomyelocele, talipes equinovarus, supernumerary tragus
3	9 weeks Male White	Bronchopneumonia	None	None
4	Newborn Male White	Congenital heart disease	Complete transposition of great arterial trunks, coarctation of aorta, patent interventricular septum	Meckel's diverticulum of ileum, harelip, cleft palate
5	Newborn Female White	Not known	Coarctation of aorta, large patent ductus arteriosus	None
6	8 years Male White	Subarachnoid hemorrhage	Coarctation of aorta	Congenital aneurysm of circle of Willis
7	9 months Female White	Bronchopneumonia	Defect in septal leaflet of mitral valve, superior vena cava on left side	None
8	20 months Female White	Tuberculous meningitis	Persistent ostium primum of interatrial septum	None
9	17 days Male White	Bronchopneumonia	Interventricular septal defect, coarctation of aorta, bicuspid tricuspid valve	None
Group II Adults (9 Cases)				
10	47 years Male Negro	Congenital polycystic kidneys, uremia	Aneurysm of membranous portion of interventricular septum	Congenital polycystic kidneys, congenital cysts of liver
11	49 years Female White	Rheumatic heart disease	None	None
12	26 years Male White	Bronchopneumonia	None	None
13	52 years Male White	Rheumatic heart disease with aortic stenosis	None	None
14	58 years Male White	Bronchopneumonia	None	Meckel's diverticulum
15	43 years Male White	Ruptured appendix, peritonitis	Coarctation of aorta, interventricular septal defect, patent ductus arteriosus, anomalous pulmonary vein entering coronary sinus	Meckel's diverticulum, congenital diverticulum of urinary bladder
16	37 years Male White	Acute pancreatitis	None	None
17	39 years Male White	Rheumatic heart disease with aortic stenosis	None	None
18	Data not available		None	Not known

There was marked predominance of males over females. Of the 9 children in group I, 6 were males, while only 1 of the 9 adults was a female.

In only 1 of the 18 cases did the condition occur in a Negro, a man.

2 *Associated Cardiac Anomalies*—In 7 of the 9 cases occurring among infants and children, there were 1 or more coexisting cardiac anomalies of the heart. In contrast, 7 of the 9 adults showed no other cardiac malformation. Coarctation of the aorta was the most frequent associated deformity, being present in 5 of the cases, while a patent interventricular septum was present in 3 instances and a patent ductus arteriosus in 2. In only 1 case, that of a newborn white girl, was there an associated anomaly probably incompatible with life, namely, complete transposition of the great arterial trunks. In 1 case there was a coexisting bicuspid pulmonary valve.

3 *Associated Extracardiac Anomalies*—Table 3 shows that the congenital bicuspid aortic valve was not associated with any particular type of extracardiac anomaly. In 6 of the 18 cases there were congenital malformations outside the heart, and these ranged from a Meckel's diverticulum of the ileum, which occurred in 3 cases, to such serious anomalies as meningocele, aneurysm of the circle of Willis and congenital polycystic kidneys.

4 *Gross Structure of the Congenital Bicuspid Aortic Valve*—Seven of the 18 aortic valves were composed of two cusps instead of three. In 6 of these one cusp was situated to the right and slightly anteriorly and showed the right coronary ostium in its sinus of Valsalva, while the other was placed to the left and posteriorly and revealed the left coronary opening in its sinus. In 4 cases the two cusps were equal in size, while in 2 instances the right coronary cusp was slightly larger than the left. Only 1 valve showed marked inequality in size of the two cusps, which measured 5 and 3 cm. in length, respectively. The larger cusp was situated to the right and anteriorly, and both the right and the left coronary ostium were found in its sinus of Valsalva.

Eleven bicuspid aortic valves showed a conjoined cusp subdivided by a congenital ridge. The data with regard to the location, dimensions and nature of the congenital ridges are shown in table 4, while table 5 records similar data with respect to the cusps.

The congenital ridge was situated at commissure A in 6 cases, at commissure B in 3 cases and at both commissures A and B in 2 cases. There was not a single instance of a congenital ridge at the site of commissure C.

Grossly the congenital ridges were similar in appearance. Each consisted of a narrow longitudinal fold of tissue which projected uniformly into the sinus of Valsalva and extended in the long axis of the aorta from the upper limit of the sinus to its floor. The lateral borders

were parallel, and the outer surface was smooth and symmetrically rounded and showed no fissure or raphe in its proximal portion. The ridges began at the upper level of the sinus in all but 2 instances, in

TABLE 4—*Nature of the Ridge in Congenital Bicuspid Aortic Valves*

Case	Location (Commissure Involved)	Dimensions,* Mm	Lateral Borders	Position in Sinus of Valsalva	Subsidiary Ridges
1	A	8 × 2 × 15	Parallel	Projects slightly and uniformly from aortic wall of sinus	Present
3	B	Not known	Parallel	Same as in case 1	Present
4	A	5 × 0.8 × 0.8	Parallel	Same as in case 1	Present
5	B	3 × 1 × 1	Parallel	Same as in case 1	Present
6	A	Data not available			
7	A	12 × 0.5 × 0.5	Not parallel	Same as in case 1	Present
9	A and B	6 × 1 × 0.5	Parallel	Same as in case 1	Present
13	A	4 × 1 × 1	Parallel	Same as in case 1	Present
16	B	12 × 2 × 2	Parallel	Same as in case 1	Present
17	A and B	A 6 × 2 × 1 B 6 × 2 × 0.5	Parallel	Same as in case 1	None
18	A	12 × 1.5 × 1	Parallel	Same as in case 1	Present

* These dimensions are always given in the following order: length, width, height

TABLE 5—*Description of Cusps in Congenital Bicuspid Aortic Valves*

Case	Location and Size of Conjoined Cusp, Cm	Location and Size of Second Cusp, Cm	Relative Size of Segments of Conjoined Cusp as Divided by Ridge	Retraction on Ventricular Aspect of Conjoined Cusp	Nature of the Cusps
1	LC and RC, 1.4	P, 1.2	Unequal	Not known	Slightly thickened
3	RC and P, 1.2	LC, 0.6	Equal	Marked	Very thick
4	LC and RC, 0.8	P, 0.8	Equal	None	Thin and delicate
5	RC and P, 1.5	LC, 0.9	Equal	Marked	Thin and delicate except adjacent to ridge
6	LC and RC, Not known	P, Not known	Equal	Not known	Slightly thickened
7	LC and RC, 1.5	P, 1.0	Unequal	Slight	Thin and delicate
9	LC and RC, 1.2 RC and P, 1.4	P, 0.8	Equal	Moderate	Moderately thickened
13	LC and RC, 2.5	P, 2.5	Equal	None	Seat of marked calcific sclerosis
16	RC and P, 4.5	LC, 2.5	Equal	None	Thickened seat of early calcific sclerosis
17	LC and RC, 4.2 RC and P, 3.5	LC, 2.5	Equal	Marked	Seat of marked calcific sclerosis
18	LC and RC, 3.5	P, 3.0	Equal	None	Thickened seat of bacterial endocarditis

which the origin was 1 mm above and 3 mm below the sinus, respectively. Terminally the main ridge was sometimes continued directly forward almost to the free margin of the cusp by a thin elevated ridge of fibrous tissue. In 2 cases the distal portion of the ridge showed a median longitudinal fissure. In 1 instance the lateral borders were converging rather than parallel.

A characteristic feature of the congenital ridge was its slight projection into the sinus of Valsalva. In 7 of the 9 cases the ridge was only 1 mm or less in height, while in 2 it was 1.5 and 2 mm in height, respectively.

In 8 cases the conjoined cusp was longer than the second cusp, in 2 cases these cusps were equal in size, while in 1 case information as to respective sizes was not available. The conjoined cusps were exactly bisected by the congenital ridge in all but 2 cases. Both of these were of combined left and right coronary cusps, and the left coronary segment was the smaller in each instance. The sweep of the ventricular aspect of the conjoined cusp was uninterrupted in 4 cases, while in 3 instances there was marked triangular retraction opposite the ridge and in 2 cases slight to moderate retraction.

5 Histologic Character of the Congenital Bicuspid Aortic Valve—When no superimposed organic disease was present, the valves consisting of two cusps with no subdividing ridge revealed a normal histologic picture, except for the presence of a thick fibrosa layer.

In the valves presenting a conjoined cusp subdivided by a congenital ridge, the latter was of chief interest histologically. Its proximal portion showed abundant elastic tissue derived from and continuous with that of the aortic media. The elastic lamellae passed uninterruptedly across the ridge and were parallel except for the central portion, where there were whorling and irregularity.

The junction between elastica and annulus fibrosus occurred in the distal segment of the ridge and usually consisted of an irregular, inverted V-shaped mass of connective tissue overlapped both superficially and deeply by the media. In 3 such cases the superficial elastica terminated at a lower level in the ridge than the deep portion, in 2 cases the deep fibers were lower, while in 2 others the lower levels were approximately the same. In 2 cases the terminal segment of elastica was entirely superficial to the annulus fibrosus and there was no deep overlap. Elastic fibers frequently extended down to the attachment of the cusp.

The annulus fibrosus consisted of dense, relatively acellular bundles of collagenous tissue arranged in a slightly irregular manner. The subsidiary ridges were composed of connective tissue both of dense collagenous type, showing slight irregularity, and of a looser mucoid variety.

None of the ridges showed significant vascularization or inflammatory change.

6 Relation of the Congenital Bicuspid Aortic Valve to Acquired Disease of the Valve—No instances of superimposed organic disease were encountered among the congenital bicuspid aortic valves occurring in infants and children. Among the 9 adults there were 2 patients with no acquired disease, while of the remaining 7, 1 had rheumatic involvement, 1 subacute bacterial endocarditis and 5 calcific sclerosis.

The patient with rheumatic disease (case 11) was a white woman aged 39 who gave a twelve year history of cardiac decompensation. At autopsy there was chronic aortic, mitral and tricuspid valvulitis with mitral and tricuspid stenosis. The aortic valve was composed of two cusps instead of three, and these were the seat of fibrous thickening and slight calcification.

Clinical data concerning the case of endocarditis lenta (case 18) are not available. Although the endocarditis was limited to the aortic valve there was microscopic evidence of both chronic aortic and chronic mitral valvulitis, probably rheumatic, in the form of numerous, thick-walled small arteries and leukocytic exudate in the free portions of the valves. The congenital ridge itself was not involved by the bacterial disease and showed no alteration grossly or microscopically.

Of the 5 patients with calcific sclerosis, 2 (cases 14 and 15) had aortic valves consisting of two cusps with no congenital ridge. The aortic lesions were not of clinical significance. In case 14 the heart showed no evidence of rheumatic disease, while in case 15 the available material was insufficient to determine the presence of rheumatic involvement.

In 3 cases calcific sclerosis was engrafted on bicuspid aortic valves which showed congenital ridges. In 1 (case 16) the condition was an incidental finding in a white man aged 38 who died of acute pancreatic necrosis and bronchopneumonia. The calcareous disease was limited to a segment of the conjoined cusp at the foot of the congenital ridge, and the rest of the valve, although thickened, was uninvolved. In the other 2 (cases 13 and 17) the patients were white men, aged 52 and 39, respectively, both of whom had clinical diagnoses of rheumatic heart disease with aortic stenosis. However, only 1, the younger, showed evidence of rheumatic disease, which was determined microscopically in both the aortic and the mitral valve. In all 3 cases none of the ridges was involved by the calcific disease.

DISTINCTION BETWEEN CONGENITAL AND ACQUIRED BICUSPID AORTIC VALVES

Occasionally the aortic valve becomes the seat of an acquired bicuspid deformity. This is produced by complete or almost complete inflammatory fusion of two adjacent cusps in the region of a commissure. After organization has occurred the fused commissural raphe is in time retracted into the sinus of Valsalva, and the retraction is accompanied by partial or almost complete obliteration of the triangular space between the fused cusps on their ventricular aspect. This results in the production of a conjoined cusp subdivided by a commissural ridge, and the resulting bicuspid valve simulates the congenital lesion.

The acquired bicuspid valve occurs especially in adults and is probably due to rheumatic fever in most instances, although in a few

cases it may be of nonrheumatic inflammatory origin. While a purely degenerative (i. e., arteriosclerotic) process may conceivably result in a bicuspid valve, this is probably rare. Six instances of acquired bicuspid aortic valve were found among the 3,300 consecutive autopsies in this survey. A gross and microscopic study of these valves was made for the purpose of comparison with the congenital lesions.

Congenital and acquired bicuspid aortic valves are not distinguishable by the character of the cusps. For example, the conjoined cusps of both lesions are similar, i. e., each is larger than or of the same size as the uncombined cusp, each is usually subdivided equally by its ridge, although occasionally the segments are unequal, and each may show slight to marked triangular retraction on its ventricular aspect opposite the ridge. In both lesions there is generally some degree of thickening of the cusps.

The location of the ridge does not necessarily aid in differentiation. In this study the congenital ridges were situated most frequently at commissure A and less often at commissure B, while all the acquired ridges were situated at commissure A. There was not a single instance of either a congenital or an acquired ridge at commissure C.

The presence of other congenital cardiac anomalies makes it more likely, but does not necessarily prove, that a given bicuspid aortic valve is congenital. Likewise, the presence of inflammatory disease of other valves indicates, without necessarily establishing, that the lesion is acquired.

The recognition of each type of bicuspid aortic valve depends essentially on distinction between a congenital and an acquired commissural ridge. In this connection it should be emphasized that even when a congenital bicuspid aortic valve becomes the seat of superimposed organic disease, the congenital ridge itself is usually not involved and hence shows little or no gross or microscopic alteration of its original structure. On the other hand, the acquired commissural ridge has a structure derived from that of two postnatally fused cusps and altered by chronic or healed inflammation.

In table 6 are shown the gross and the microscopic character of each type of ridge. In the acquired lesion the ridge is usually only moderately depressed in the sinus of Valsalva and less so distally, near the free margin of the cusp, than in the proximal portion, so that when viewed laterally its course in the sinus is oblique from above downward. The lateral surfaces diverge in the distal portion, which is thus wider than the proximal portion. Although the outer surface is frequently smooth and rounded, it may show a fissure proximally indicating the line of fusion of the two adjacent cusps. In contrast, the congenital ridge consists of a sharply outlined, hemicylindric elevation of the aorta in the sinus of Valsalva, with parallel lateral borders and a smooth, sym-

metrically rounded outer surface. The ridge projects uniformly and only slightly into the sinus of Valsalva and descends almost vertically from the upper limit of the sinus to its floor. While the acquired bicuspid valve may show shortening of the circumference of its free margin, the inlet of the valve is usually not reduced in the congenital lesion.

Microscopically, the acquired ridge shows no distinct layer of elastica, although a few strands of elastic tissue may be present, especially at the sides. It is composed essentially of connective tissue the base of which

TABLE 6—*Distinction Between Congenital and Acquired Ridges in Bicuspid Aortic Valves*

Congenital Ridge		Acquired Ridge
A Gross Criteria		
1	Ridge projects only slightly into sinus of Valsalva, and projection is uniform throughout its length	Ridge projects farther into sinus of Valsalva, and distal portion shows greater elevation than proximal
2	Course in sinus of Valsalva is vertical and in long axis of aorta	Course is oblique and does not parallel long axis of aorta
3	Lateral borders are sharply defined and parallel	Lateral borders are not sharply defined, and lateral surfaces usually diverge from above downward
4	Outer surface is smooth, symmetric and hemicylindric, with no fissure or raphe in proximal portion	Outer surface is not hemicylindric and may show a fissure in its proximal portion
5	Subsidiary ridges are usually present at termination of main ridge	No subsidiary ridges are present
B Microscopic Criteria		
1	There is elevation of aortic media into ridge, together with whorled pattern of elastica and low insertion into annulus fibrosus	No significant elastica is present in the ridge
2	Normal aortic media annulus fibrosus relationship is altered	Normal relationship of aortic media to annulus fibrosus is preserved
3	The architecture is symmetric, owing to continuity of the various layers across ridge	Usually no distinct continuity of layers across ridge is present
4	There is no significant vascularization or inflammation	Vascularization and inflammation may be present

rests on the aortic media, thus preserving the aortic media-annulus fibrosus relationship of the normally developed commissure. The connective tissue is densely fibrous, hyalinized and relatively acellular. Although usually irregular in arrangement, yet in some instances, especially in the most proximal segment, it appears to pass across the ridge without interruption. The fibrosis is generally so extensive that all vestige of the original outline of the two fused cusps forming the ridge is lost. Chronic or acute inflammation may be present. Vascularization is often absent or difficult to demonstrate in the proximal portion of the ridge, but is present in the form of capillaries and arterioles in the distal segment.

In contrast, the congenital ridge shows numerous elastic laminae continuous with the aortic media. These are elevated into the ridge and pass uninterruptedly across it in a parallel and symmetric manner.

except in the central portion, where there is irregularity and whirling. The elastica frequently descends to the attachment of the cusp. At its junction with the annulus fibrosus the media is superficial to the connective tissue, and this is the reverse of the usual relationship. No vascularization or cellular exudate is present.

COMMENT

Abbott⁷ pointed out that the congenital bicuspid aortic valve is likely to be accompanied by "minor" anomalies on the left side of the so-called acyanotic or *cyanose tardive* group, such as coarctation of the aorta, patent ductus arteriosus and patent interventricular septum. Coexisting coarctation is especially frequent. Conversely, among 200 cases of coarctation of the aorta, Hamilton and Abbott⁸ found 51 instances of congenital bicuspid valve. Abbott stated that such serious defects as transposition of the great vessels and pulmonic stenosis are rarely associated with the valvular anomaly. This is true of the present series, in which there was only 1 case of transposition of the arterial trunks.

In 9 cases, i. e., 2 of infants and 7 of adults, no other cardiac anomalies were present. Although not yet verified statistically, the high incidence of uncomplicated lesions among adults is probably due to failure of infants and children with coexisting cardiac or serious extra-cardiac anomalies to survive.

Simple bicuspid valves can readily be identified, but it is difficult to distinguish between those forms with congenital fusion and those with fusion due to acquired disease. The conjoined cusps themselves, with respect to location of fusion, size or general appearance, provide no satisfactory data for purposes of distinction, and Osler's criteria⁹ based on these features are inadequate. The differentiation depends on the gross and microscopic character of the congenital ridge and of the acquired commissural raphe. The distinguishing features have been described in the preceding section.

In 1923, Lewis and Grant¹ compared the congenital and the acquired lesions with respect to the distribution of the elastic tissue of the aortic media and its relation to the annulus fibrosus. The congenital ridge was found to contain elastic lamellae derived from the aorta, and in the

7 Abbott, M. E. On the Relative Incidence and Clinical Significance of a Congenitally Bicuspid Aortic Valve, with Five Illustrative Cases, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 1, p. 1.

8 Hamilton, W. F., and Abbott, M. E. Complete Obliteration of the Descending Arch at Insertion of the Ductus in a Boy of Fourteen, Bicuspid Aortic Valve, Impending Rupture of the Aorta, Cerebral Death, *Am Heart J* 3:381, 1928.

9 Osler, W. The Bicuspid Condition of the Aortic Valves, *Tr. A. Am Physicians* 1:185, 1866.

center of the ridge these showed a whorling configuration. Furthermore, the elastica had an abnormally low insertion into the annulus and frequently terminated superficial to the annulus. In inflammatory fusion the usual commissural aortic media-annulus fibrosus relationship was preserved, that is, the annulus was superficial to the elastica. The work of Bishop and Trubek¹⁰ substantiated that of Lewis and Grant.

The microscopic observations in the present study are generally confirmatory of those of Lewis and Grant and of Bishop and Trubek, but since sections were made both transversely and longitudinally, the results provide additional information. Attention is directed to the following considerations of the microscopic features of the congenital ridge: (1) the presence in the entire proximal portion of elastic tissue continuous with the aortic media, (2) the whorling of the elastica seen in transverse sections, (3) the descent of the elastic tissue to a low level in the ridge, frequently as far as the attachment of the cusp, (4) the junction of elastica and annulus fibrosus, this usually taking the form of an inverted V with elastic fibers overlapping the annulus both superficially and deeply (either the superficial or the deep extensions of elastic tissue may terminate at a lower level in the ridge), and (5) the absence of unusual vascularization and inflammation. The last is of importance because even in cases of superimposed organic valvular disease the congenital ridge appears not to be significantly altered. In the majority of instances the superficial elastica terminated at a lower level than the deep elastic tissue.

Recently Gross¹¹ expressed the belief that practically all bicuspid aortic valves in adults are the result of acquired disease. This conclusion was based on the claim that in children the bicuspid valves which were undoubtedly congenital differed from those in adults. This view is at variance with the results of the present study and could not be confirmed.

Congenital bicuspid aortic valves are of clinical significance only in their relation to the development of superimposed organic disease. According to the literature bacterial endocarditis is the only disease frequently engrafted on these valves. For example, Lewis and Grant,¹ who found 8 congenital bicuspid aortic valves among 31 consecutive cases of subacute bacterial endocarditis, estimated that in 23 per cent of all adults with this anomaly bacterial endocarditis develops. In the series observed in the present study only 1 of 9 adults showed endocarditis lenta. Moreover, the heart was the seat of rheumatic disease, and this, rather than the congenital lesion, may have predisposed to the develop-

10 Bishop, L. F., Jr., and Trubek, M. Bicuspid Aortic Valve. A Differential Study Between Inflammatory and Congenital Origin, *J. Tech. Methods* **15** 111, 1936.

11 Gross, L. So-Called Congenital Bicuspid Aortic Valve, *Arch. Path.* **23** 350 (March) 1937.

ment of the endocarditis. This also applies to the hearts studied by Lewis and Grant, in most of which the lesions were of rheumatic origin. A significant relationship between congenital bicuspid aortic valves and endocarditis lenta can be established only when rheumatic heart disease is excluded.

Of the 7 adults with superimposed organic disease, 3 showed rheumatic involvement. In 1 there was gross aortic, mitral and tricuspid valvulitis, while in 2 others, i. e., patients with endocarditis lenta and calcific sclerosis of the aortic valve, respectively, microscopic examination showed rheumatic disease of the aortic and mitral valves. It is also possible that 1 or more of 4 other aortic valves with calcific sclerosis may have been the seat of isolated and healed rheumatic disease. The number of cases available is obviously too small to permit a statement as to whether congenital bicuspid aortic valves show a predilection to rheumatic involvement.

Syphilitic aortic valvulitis was not found in this series, but Richter¹² reported a case of the association of syphilitic involvement and congenital bicuspid aortic valve, and I have observed such a case at another hospital.

Although there was calcific sclerosis in 5 of the 9 adults in this series, 1 had rheumatic disease and the possibility of that or other inflammatory disease in the remaining 4 cannot be positively excluded. Nevertheless, the possibility that the congenital lesion alone may be significant in the development of the calcareous disease deserves further consideration.

The inherent tendency of congenital bicuspid aortic valves to undergo degeneration and fibrosis has been pointed out frequently and is attributed to the fact that the abnormally developed cusps are composed of imperfect or defective tissue. Uncomplicated lesions in adults, and even those in infants and children, frequently lack the thin translucent character of the normal valve and consist of thickened and fleshy cusps. The degeneration and fibrosis are undoubtedly accelerated with age, and in older persons, particularly those with an especial tendency to arteriosclerosis, would be prone to lead to the deposition of calcium.

From my experience it appears likely that the association of calcific sclerosis with congenital bicuspid aortic valve is not as rare as a survey of the literature would indicate. This seems especially true since a certain number of persons with congenital bicuspid aortic valve undoubtedly survive to the period of life when arteriosclerosis is prevalent. Both Lewis and Grant¹ and Bishop, Bishop and Trubek¹³ report 1

12 Richter, A. B. Treponema Pallidum in Syphilitic Aortic Valvulitis of a Congenitally Bicuspid Valve with Subaortic Stenosis, *Am J Path* **12** 129, 1936.

13 Bishop, L. F., Bishop, L. F., Jr., and Trubek, M. Aortic Stenosis of Inflammatory Origin, with a Differential Study of the Acquired or Congenital Origin of a Bicuspid Aortic Valve, *Am J M Sc* **188** 506, 1924.

instance of calcific sclerosis in their series of 11 and 9 cases, respectively, of congenital bicuspid aortic valve

SUMMARY

In a survey of 3,300 consecutive autopsies, congenital bicuspid aortic valve was found in 18 cases (0.54 per cent) and was the most common single cardiac anomaly. In 9 cases it occurred in infants and children and in 9 adults, 14 of the patients were male and 4 female, and 7 of the adults were more than 35 years old. Next in order of incidence were coarctation of the aorta (16 cases) and patent interventricular septum (14 cases). The most frequent associated cardioaortic anomalies were coarctation of the aorta, patent interventricular septum and patent ductus arteriosus, but in 9 of the 18 cases the bicuspid aortic valve was the only congenital deformity in this region. In 1 instance there was also bicuspid pulmonic valve.

In 7 cases simple bicuspid valves were present, but in 11 instances there was congenital fusion of two cusps, the resultant ridge being at commissure A in 6 cases, at commissure B in 3 cases and at both commissures in 2 cases, no fusion was found at commissure C. In 9 cases the conjoined cusp was larger than the other cusp. The congenital ridge divided the conjoined cusp equally in all but 2 cases. Retraction of the ventricular aspect of the conjoined cusp opposite the ridge occurred in 5 cases.

So distinctive as to be practically pathognomonic is the gross character of the ridge, a narrow, hemicylindric, barlike elevation situated at the commissure, directed in the long axis of the aorta and extending slightly into the sinus of Valsalva, sharply defined, with parallel borders, and devoid of fissures at the proximal portion. The microscopic picture is characteristic. The ridge consists almost entirely of elastica, whorled centrally and continuous laterally with that of the aortic media, the elastica usually overlaps the annulus fibrosus superficially and deeply or only superficially. Blood vessels are scanty, and there is no inflammation.

The commissural raphe of acquired bicuspid aortic valve differs in that it is constituted largely of relatively acellular collagenous tissue, has little or no elastica and shows the presence or residues of other disease.

Superimposed disease of the aortic valve was not found in any of the cases in early life, but in the form of rheumatic involvement, endocarditis lenta or calcific sclerosis it was present in 7 of the 9 adults. It is only with the greatest rarity that the superimposed disease actually affects the congenital ridge. The study also suggests that this congenital anomaly may predispose to calcific sclerosis.

ACQUIRED BICUSPID AORTIC VALVES

SIMON KOLETSKY, M D

CLEVELAND

A recent survey of 3,500 consecutive autopsies at the Institute of Pathology of the University Hospitals of Cleveland revealed 8 cases of acquired bicuspid aortic valve. This paper comprises a study of these cases, with especial reference to the cause and significance of the acquired bicuspid aortic valve.

REPORT OF CASES

CASE 1—A 41 year old white man had clinical diagnoses of endocarditis lenta and aortic stenosis and insufficiency. There was no history of rheumatic fever, although the patient was told by a physician thirteen years prior to admission that he had heart disease. The heart was enlarged and revealed a systolic thrill at the base, a loud, harsh systolic murmur and a diastolic murmur over the aortic area and a systolic murmur at the apex.

The heart weighed 490 Gm. There were coarse fibrous adhesions between the aorta and the pulmonary artery, in the atrioventricular sulcus and between the layers of pericardium at the base. Acute fibrinous pericarditis was also present. The mitral and tricuspid valves showed slight diffuse thickening.

The aortic valve consisted of two thickened cusps of equal size with calcific nodules projecting from both aortic and ventricular surfaces. There was complete fusion of the left and right coronary cusps to form a single conjoined cusp subdivided at commissure A¹ by a depressed, fibrous, calcified raphe, which appeared to hold the conjoined cusp rigidly away from the aortic wall so as to cause considerable stenosis of the ostium. The noncoronary cusp showed friable, poorly organized vegetations on both the aortic and the ventricular aspect.

Microscopic sections of the aortic valve showed calcific deposits in the ring and cusp, as well as organizing vegetations characteristic of endocarditis lenta². Sections of the mitral and tricuspid valves revealed chronic and subacute interstitial valvulitis with fibrosis, vascularization and exudation of leukocytes. Numerous sections of myocardium showed extensive scarring and both diffuse and focal leukocytic infiltration but no definite Aschoff bodies. No sections of the fused commissural raphe were made.

From the Institute of Pathology, Western Reserve University and University Hospitals.

1 The following nomenclature of the aortic valve is used. The aortic cusps are designated according to the situation of the coronary arteries as the left coronary (LC), the right coronary (RC) and the noncoronary, or posterior, (P) cusps. The left coronary-right coronary commissure is referred to as commissure A, the right coronary-posterior commissure as commissure B and the left coronary-posterior commissure as commissure C.

2 Microscopic sections were studied with the hematoxylin and eosin stain and with the Weigert technic for elastic tissue.

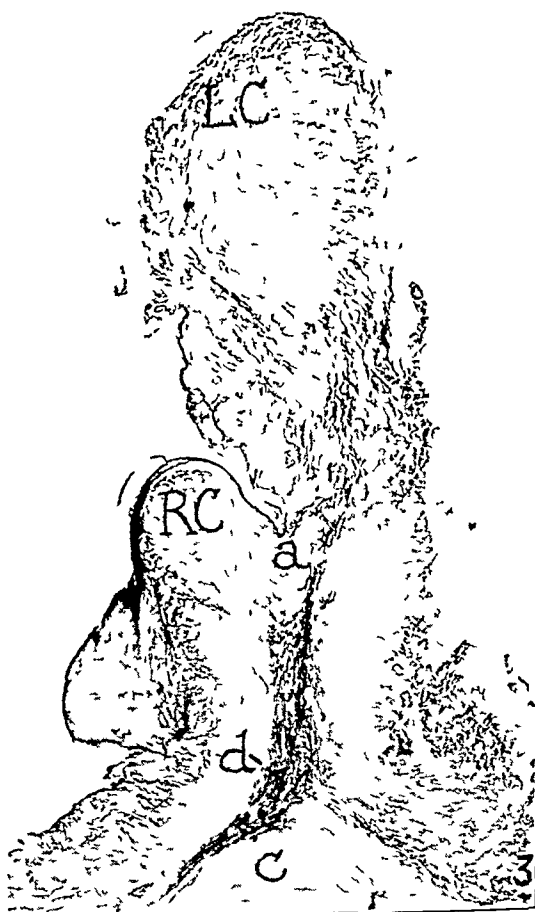
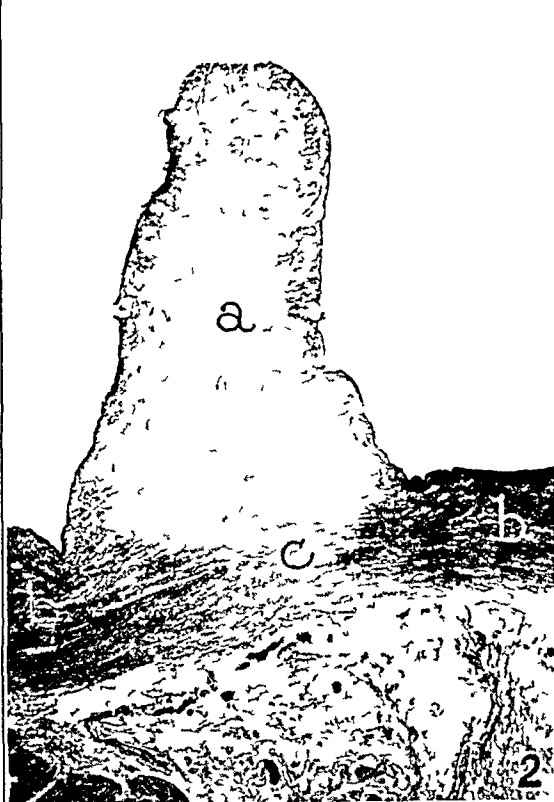
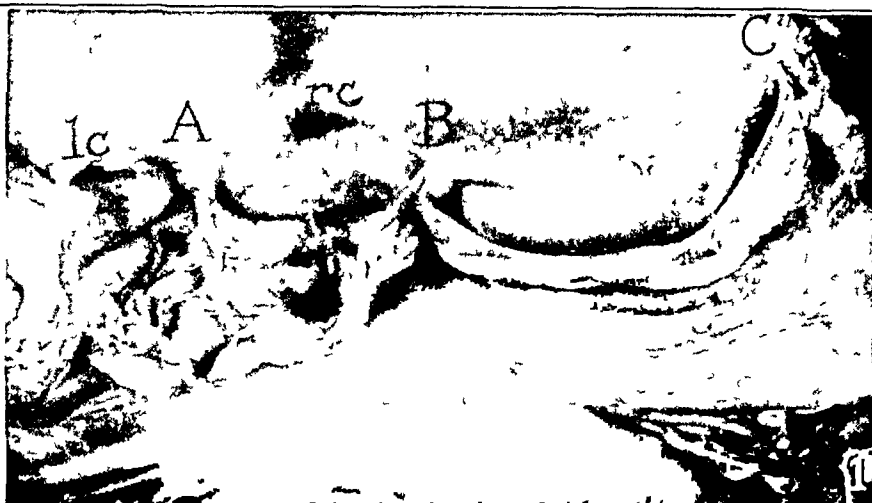


Figure 1

(See legend on opposite page)

CASE 2—A 21 year old Negro died on the second day after an appendectomy. Physical examination of the heart revealed nothing abnormal.

The heart weighed 330 Gm., and the only gross pathologic change was a bicuspid aortic valve (fig 11). One cusp was a combined left and right coronary cusp, 3.2 cm long, while the other was a noncoronary cusp, 2.8 cm in length. The conjoined cusp was evenly subdivided at commissure A by a longitudinal ridge, measuring 10 by 1 by 2 to 4 mm (fig 2) and extending obliquely downward from the upper level of the sinus of Valsalva to a point 2 mm beyond the attachment of the cusp. The outer surface was smooth and rounded and showed a longitudinal fissure in its middle half. In this region there was retraction of the right coronary cusp, so that the free margin and outer portion of the raphe were formed entirely by the left coronary cusp. There was irregular fibrous thickening of the conjoined cusp beyond the termination of the ridge with inward rolling of the free margin. The coronary ostiums were situated symmetrically on either side of the ridge in their usual positions. Commissures B and C showed no abnormality.

Serial transverse microscopic sections were made of the commissural raphe. In the proximal portion (fig 12) the raphe consisted of dense bundles of collagenous connective tissue resting on aortic media and showing no vascularization or cellular exudate. In the distal portion the structure was similar but more delicate and suggested the original outline of the two fused cusps. There was considerable retraction of the right coronary arm of the raphe toward the valvular ring. Vascularization was present only distally and basally, just above the subvalvular endocardium, in an area of fibrosis situated centrally with respect to the lateral borders, involving the ventricularis layers and showing numerous irregularly disposed elastic fibers, probably derived in part from these layers (fig 13). Capillaries and arterioles were present, as well as edema and exudation of lymphocytes and occasional polymorphonuclear leukocytes. The rest of the raphe showed no significant elastica.

EXPLANATION OF FIGURE 1

Fig 1—Case 2, a 21 year old Negro 1, the aortic valve is bicuspid and shows a raphe at commissure A. There is fibrous thickening of the conjoined cusp beyond the termination of the raphe with inward rolling of the free margin. In this photograph and in figures 41 and 71, the aortic valve is approximately one and one-half times the actual size. In figures 3, 51 and 6, the valve is approximately the actual size. In all photographs of the aortic valve, A represents the left coronary-right coronary commissure, B the right coronary-posterior commissure and C the left coronary-posterior commissure, while *lc* and *rc* indicate the ostiums of the left and the right coronary artery, respectively. 2, transverse microscopic section of the proximal portion of the commissural raphe. The raphe consists of dense bundles of collagenous connective tissue (*a*) resting on aortic media (*b*) and subvalvular endocardium (*c*) and showing no vascularity or inflammation. Weigert elastica stain, $\times 15$. 3, transverse microscopic section of the distal portion of the raphe. The structure is similar to that of the proximal part and suggests the original outline of the two fused cusps. There is considerable retraction of the right coronary cusp (*RC*), so that the outer portion and free margin of the raphe are formed solely by the left coronary cusp (*LC*). Vascularity and inflammation are present in the area (*d*) just above the subvalvular endocardium (*c*). This area contains numerous delicate elastic fibers. Weigert elastica stain, $\times 15$.

Numerous sections of the conjoined cusp showed fibrosis of the ventricularis layer, especially near the line of closure, but no vascularity or acute inflammation. The auricularis and spongiosa layers of the mitral valve were also slightly thickened. Sections of the tricuspid and pulmonary valves showed nothing abnormal. Sections of both ventricles and of the left atrium showed numerous small perivascular fibrous scars, but there were no Aschoff bodies.

CASE 3—A 68 year old white man had clinical diagnoses of generalized arteriosclerosis and hypertension, aortic stenosis and insufficiency and bronchopneumonia. There was enlargement of the heart, and a systolic thrill was felt in the aortic area. A loud, rough systolic murmur transmitted to the neck and a soft diastolic murmur were heard over the aortic area.

The heart weighed 670 Gm. Both mitral leaflets were thickened, but there was no fusion at the commissures. The tricuspid and pulmonary valves showed no abnormality. The aortic valve was bicuspid as a result of complete fusion of the left and right coronary cusps, resulting in a conjoined cusp. This was of the same size as the noncoronary cusp. The raphe formed at commissure A.

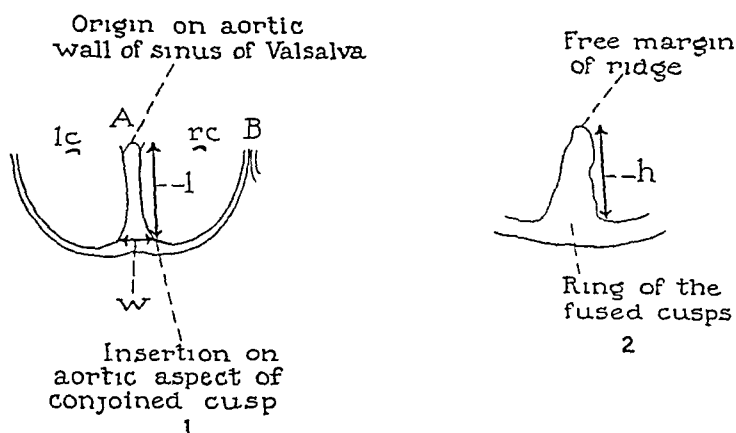


Fig 2—Diagram illustrating the dimensions of a commissural raphe. 1, view of the aortic valve from above, showing a raphe at commissure A, l denoting the length of the raphe from its origin on the aortic wall of the sinus of Valsalva to its insertion on the aortic aspect of the conjoined cusp. 2, a transverse section of the raphe (perpendicular to its long axis), h , denoting the height of the raphe from the ring of the fused cusps to the free margin.

by fusion had the form of a longitudinal ridge, narrow in its proximal portion but wider distally, where it merged with the conjoined cusp several millimeters below the free margin. Both cusps were rigid and immobile and showed extensive thickening and calcification, especially in the outer portions. As a result the orifice of the valve was reduced to a narrow slit. The coronary ostia were situated in their usual locations on either side of the ridge. Commissures B and C showed no abnormality.

Microscopic sections of the aortic valve showed marked hyalinization and nodular deposit of calcium in the ring and outer portion of the cusps near the free margin. There was calcific erosion on the aortic aspect of the cusps. Capillaries and arterioles were present, chiefly in the ventricularis and arterial layers, but there was no inflammation. Sections of the mitral valve revealed vascularization,

calcification and ossification in the ring. The free portions of the leaflets showed focal vascularization of the spongiosa layer in the form of capillaries and arterioles.

No sections of the fused commissural raphe were made.

CASE 4—A 68 year old white man died of carcinoma of the kidney with extensive metastases. Examination of the heart revealed slight enlargement to the left, a precordial systolic murmur, loudest over the aortic area, and a systolic thrill in the same region. A clinical diagnosis of calcific sclerosis of the aortic valve with stenosis was made.

The heart, the seat of hypertrophy and dilatation, weighed 510 Gm. The mitral, tricuspid and pulmonary valves were normal macroscopically. The aortic valve consisted of two cusps of equal size (fig 3). One was a combined left and right coronary cusp which was divided into two equal portions by a ridge at the site of commissure A. This ridge was narrow in its proximal half but considerably wider and deeper distally, owing to divergence of the lateral borders.

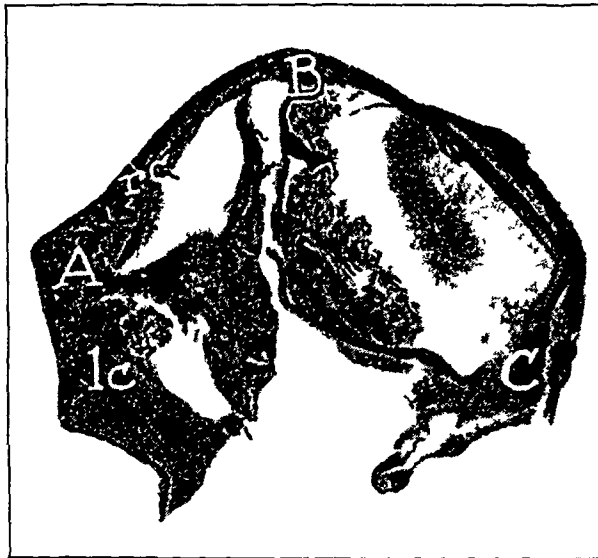


Fig 3—Case 4, a 68 year old white man with calcific sclerosis of an acquired bicuspid aortic valve. The raphe at commissure A has an oblique course in the sinus of Valsalva and is wider distally than proximally. The distal half is calcified. There is also considerable calcification of the cusps, especially the aortic aspect of the noncoronary cusp.

It extended obliquely downward and forward from the upper margin of the sinus of Valsalva and terminated by merging almost imperceptibly with the conjoined cusp several millimeters below the line of closure. Its outer surface was smooth and showed no trace of a fissure. The distal half showed considerable thickening and calcification. There was slight retraction of the ventricular aspect of the conjoined cusp opposite the ridge. Commissures B and C showed no significant change.

Both cusps were the seat of fibrosis and calcific deposit, especially the conjoined cusp, the free margin of which adjacent to the commissural raphe showed inward rolling. There were calcific excrescences in both sinuses of Valsalva, and the entire aortic surface of the noncoronary cusp was studded with nodular calcific deposits, which were more numerous near the free margin than at the base. A

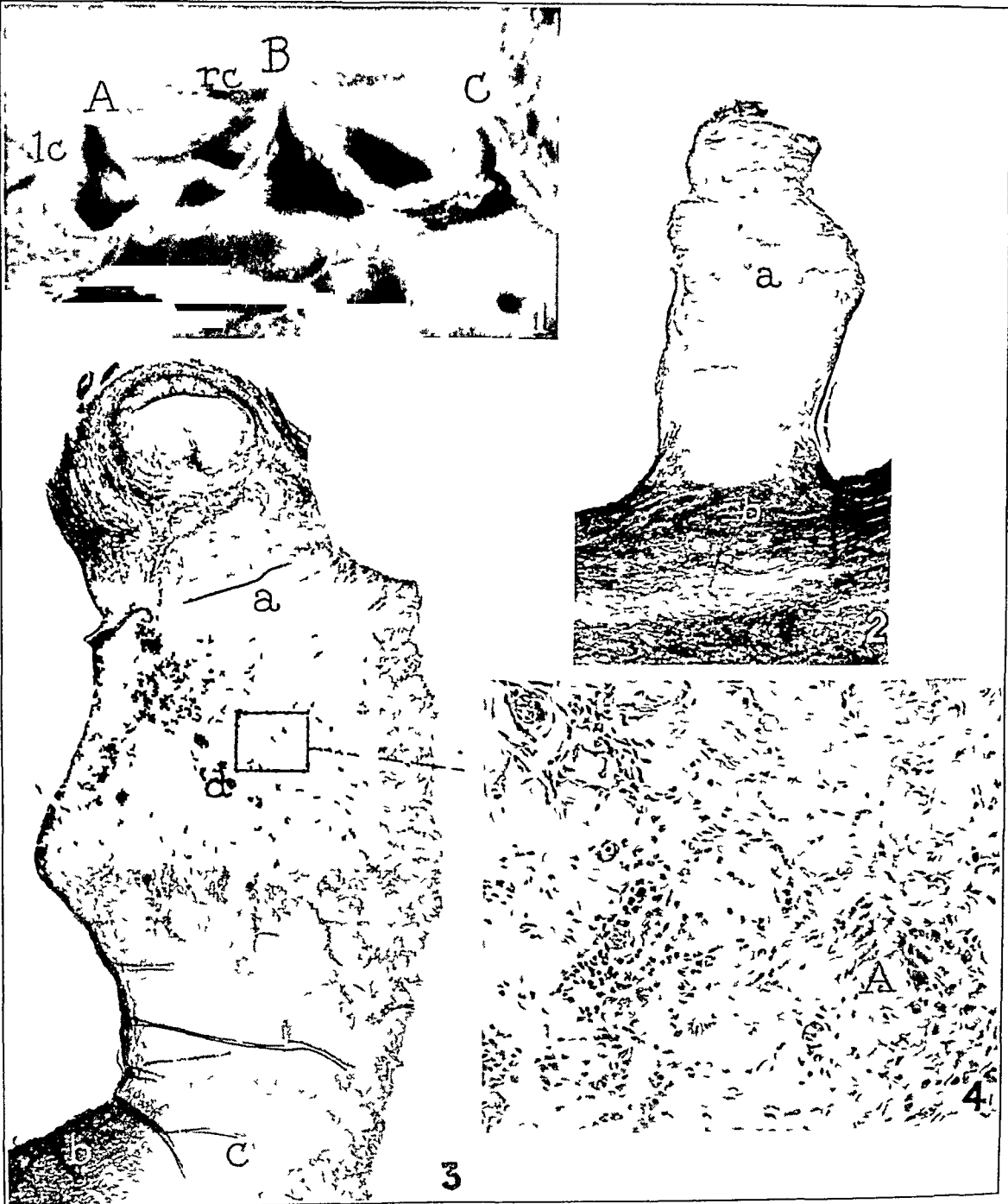


Figure 4

(See legend on opposite page)

few similar nodules projected from the ventricular aspect of the cusp, and erosion was present on both surfaces

Transverse microscopic sections of the fused commissural raphe revealed densely fibrous and largely acellular connective tissue, which in its proximal portion rested on aortic media and showed no vascularity or inflammation. There was only a suggestion of the original margins of the two fused cusps. Distally the fibrous tissue was partly hyalinized and calcified. In the basal portion, just above the subvalvular endocardium, there were areas of less mature fibrous tissue which showed vascularization in the form of capillaries and arterioles, edema and exudation of lymphocytes, occasional plasma cells and polymorphonuclear leukocytes. The vascularity and inflammation were situated in the central two thirds of the ridge and extended to within a short distance of the lateral borders. The only elastic tissue present in the raphe consisted of several continuous subendothelial strands in the arterialis layers and a small number of irregularly disposed delicate fibers in the areas of fibrosis and inflammation.

Sections of the aortic cusps revealed fibrosis and vascularity of the ring and marked fibrous and hyaline thickening of the free portions. All the layers of the cusp were involved, especially the arterialis and ventricularis, which showed focal and confluent nodules of calcium and fragments of bone. No exudate was present, but there was vascularization with capillaries and arterioles, particularly of the ventricularis layer. In general, the calcification was most extensive in the distal portion of the arterialis layer.

Sections of the mitral valve revealed fibrous thickening of the various layers, especially near the free margin. In one section of the septal leaflet there was an area in the auricularis layer showing edema, lymphocytic exudate and several capillaries.

The ventricles, atria and tricuspid valve showed no evidence of rheumatic disease.

Sections of the pulmonary valve showed considerable fibrous thickening, arteriolar vascularization and lymphocytic exudate in the ventricularis layer.

CASE 5—A 13 year old boy died of acute rheumatic heart disease with mitral and aortic insufficiency. There was a history of rheumatic fever at the age of 9.

EXPLANATION OF FIGURE 4

Fig 4—Case 5, a 13 year old white boy with an acquired bicuspid aortic valve, which is the seat of chronic and superimposed acute rheumatic valvulitis. 1, the raphe at commissure *A* is narrow and uniform in width and is attached to the conjoined cusp halfway toward the free margin. Commissures *B* and *C* show no change. 2, transverse microscopic section of the proximal portion of the commissural raphe. The raphe consists of compact, hyalinized connective tissue (*a*) resting on aortic media (*b*) and showing no vascularity or inflammation. Weigert elastica stain, $\times 15$. 3, transverse microscopic section of the distal portion of raphe. The raphe (*a*) rests on subvalvular endocardium (*c*), with aortic media (*b*) inserting into the base laterally. There are extensive fibrosis, vascularity and inflammation in the middle third (*d*) of the ridge. Nodular fibrous whorling and elastification are present along the free margin. Weigert elastica stain, $\times 16$. 4, area marked *d* in figure 3. An Aschoff body is shown at *A*. Hematoxylin and eosin, $\times 116$.

The heart, the seat of hypertrophy and dilatation, weighed 430 Gm. There were stenosis of the mitral and tricuspid valves and acute verrucous endocarditis of both these valves and of the aortic valve. The pulmonary valve showed no significant change. The aortic valve was bicuspid, consisting of a large cusp, 3 cm in length, formed by complete fusion of the left and right coronary cusps and a smaller noncoronary cusp, 2 cm long (fig 41). The conjoined cusp was evenly subdivided at commissure A by a narrow longitudinal ridge measuring 10 by 1 by 1 to 3 mm. This was considerably depressed in the sinus of Valsalva and extended obliquely from the upper level of the sinus to a point on the aortic aspect of the cusp, halfway toward the free margin. The ridge was uniform in width throughout its length and was of greater height distally than proximally. Its outer surface was smooth and rounded and showed no fissure. There were shortening and appreciable fibrous thickening of both cusps, especially of the conjoined cusp in the vicinity of the commissural raphe. The ventricular aspect of the conjoined cusp showed distinct triangular retraction opposite the ridge. The coronary ostia occupied their usual positions. Commissures B and C showed no abnormality.

Serial transverse microscopic sections of the ridge revealed complete blending of the two fused cusps, with little trace of the original margins. The proximal portion was composed of moderately compact and partly hyalinized connective tissue, which showed no vascularity or inflammation (fig 42). In the distal half there were extensive fibrosis, with numerous elastic fibers, many capillaries and arterioles, exudation of lymphocytes, plasma cells and polymorphonuclear leukocytes and Aschoff bodies. Although these changes were diffuse, they were more noticeable in the middle third of the ridge than in the basal portion or near the free margin (fig 43 and 4).

Microscopic sections of the aortic, mitral and tricuspid valves showed lesions typical of chronic and superimposed acute verrucous rheumatic inflammation. The ventricles and atria revealed numerous Aschoff bodies.

CASE 6—A 74 year old white man died of primary carcinoma of the lung. The heart appeared slightly enlarged on percussion, and a systolic murmur was present over the precordium and heard best in the aortic area.

The heart weighed 340 Gm. The mitral, tricuspid and pulmonary valves showed no abnormality. The aortic valve was bicuspid, and the left and right coronary cusps were fused to form one large cusp, 4.5 cm long, as compared with the noncoronary cusp, which had a length of 3.5 cm (fig 51). Commissure A was replaced by a markedly depressed ridge, measuring 12 by 1 to 3 by 1 to 3 mm, which divided the conjoined cusp into a small left coronary segment, 1.5 cm long, and a larger right coronary segment, 3 cm long. The coronary ostia occupied their usual positions in relation to their corresponding cusps.

The course of the fused commissural raphe in the sinus of Valsalva was oblique, and it extended from the upper level of the sinus to a point halfway to the free margin of the cusp. The outer surface was irregular, especially in the distal portion, but no trace of a fissure was present. Thick and calcified folds of tissue, evidently representing the left and right coronary cusps, joined the lateral aspect of the ridge near its center. The distal half of the ridge, as well as the adjacent aortic aspect of the conjoined cusp, showed calcific nodules. There was distinct retraction on the ventricular aspect of the conjoined cusp opposite the ridge.

Both aortic cusps were the seat of thickening and calcification. This involved both the basal portion and the free margin, especially the latter, and both the aortic



Fig 5—Case 6, a 74 year old white man with calcific sclerosis superimposed on an acquired bicuspid aortic valve 1, commissure *A* is replaced by a calcified ridge which divides the conjoined cusp into a small left coronary and a larger right coronary segment Commissures *B* and *C* show no change 2, transverse microscopic section of the proximal portion of the raphe at commissure *A* The raphe consists of dense hyalinized connective tissue (*a*) showing atheromatous degeneration and resting on aortic media (*b*) There is no vascularity or inflammation A few strands of elastica pass across the ridge in a subendothelial position Weigert elastica stain, $\times 10$ 3, transverse microscopic section of the distal portion of the raphe The raphe (*a*) rests on subvalvular endocardium (*c*) with aortic media (*b*) inserting laterally at the base on both sides There are calcification in the outer portion of the ridge and also nodular fibrosis and elastification An area of irregular fibrosis, vascularity and inflammation (*d*) is shown in the basal and middle thirds of the raphe This area contains numerous delicate elastic fibers Weigert elastica stain, $\times 10$ *d*, area marked *d* in 3, hematoxylin and eosin, $\times 114$

and the ventricular aspect. Calcific nodules were present on the ventricular aspect of the aortic leaflet of the mitral valve and in the intervalvular fibrosa.

Serial transverse microscopic sections of the commissural raphe were made. The proximal portion consisted of dense, almost acellular, hyalinized fibrous tissue with numerous foci of atheromatous degeneration, which rested on the aortic media (fig 52). A few strands of elastic tissue passed continuously across the ridge in a subendothelial position. There was no vascularity or inflammation. In the distal half the original margins of the two fused cusps could be partly visualized, although there were marked hyalinization and calcification. In the basal and middle thirds of the ridge, between the subvalvular endocardium and the free margin, there were areas of irregular fibrosis showing numerous delicate elastic fibers, vascularization in the form of arterioles and capillaries and exudation of small round cells and polymorphonuclear leukocytes (fig 53 and 4). This occurred throughout the central portion and appeared to involve all but the arterial layers. Near the free margin there were considerable whorling of

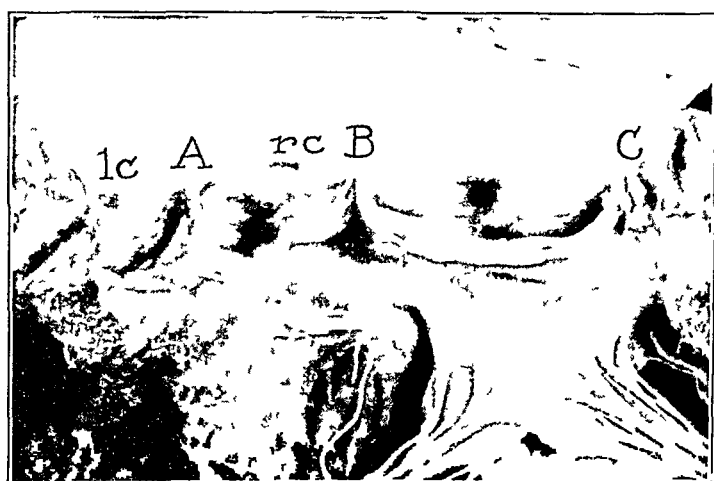


Fig 6—Case 7, a 49 year old white woman with an incidental acquired bicuspid aortic valve. The two aortic cusps are equal in size, and the conjoined cusp is evenly subdivided by the raphe at commissure *A*. Commissures *A* and *B* show no change.

fibrous tissue and an abundance of delicate elastica. Longitudinal sections of the conjoined cusp adjacent to the ridge showed fibrous thickening and calcific nodules, especially near the line of closure, with vascularity and lymphocytic exudate in the ventricularis and spongiosa layers. Other sections of the conjoined cusp, as well as those of the noncoronary cusp, disclosed similar changes.

Sections of the mitral valve showed fibrous thickening of the substance of the leaflet and vascularization of the auricularis layer in the form of capillaries and arterioles. Sections of the tricuspid and pulmonary valves revealed no significant abnormality.

CASE 7—A 49 year old white woman died of malignant neutropenia. Physical examination of the heart revealed nothing abnormal.

The heart weighed 370 Gm, and the only significant abnormality was a bicuspid aortic valve (fig 6). The mitral, tricuspid and pulmonary valves were normal. The two aortic cusps were equal in size, each measuring 3.5 cm in length. One

was a combined left and right coronary cusp, while the other was the noncoronary cusp. The conjoined cusp was subdivided evenly at commissure A by a ridge of firm tissue which extended obliquely from the upper level of the sinus of Valsalva to a point midway between the base and the free margin of the cusp. The outer surface was smooth and rounded and showed no trace of a fissure. The distal segment was wider and deeper than the proximal. There was moderate thickening of the free margin of the conjoined cusp adjacent to the ridge, and a distinct retraction was present on the ventricular aspect of the cusp opposite the ridge. The coronary ostiums were situated on either side of the ridge in their normal locations. Commissures B and C showed no significant change.

The aorta and coronary arteries were almost entirely free of arteriosclerosis.

Longitudinal microscopic sections of the commissural raphe showed that it was composed of dense collagenous connective tissue, partly hyalinized and largely acellular. In its proximal half this tissue rested on the aortic media and in its distal half on the subvalvular endocardium. Vascularization was present only in the distal and basal portion of the ridge, directly above the subvalvular endocardium. The vessels consisted of capillaries, thick-walled small arteries and arterioles and were contained in an edematous, fibrous stroma, which showed slight infiltration of lymphocytes and polymorphonuclear leukocytes. Sections of the conjoined and noncoronary cusps showed fibrous thickening of all layers, especially of the ventricularis; this was most marked near the free margin of the conjoined cusp adjacent to the ridge. However, there was no vascularity or inflammation.

Sections of the mitral valve showed fibrous thickening of the auricularis layer, which contained several thick-walled small arteries and arterioles. There was no exudation of leukocytes. The ring of the valve was also well vascularized. Sections of the tricuspid valve revealed capillaries and arterioles, both in the ring and in the auricularis and spongiosa layers of the free portion, together with infiltration of small round cells.

CASE 8—A 63 year old white man died of cardiac failure. The clinical diagnoses were hypertension, calcific sclerosis of the aortic valve with stenosis and remote myocardial infarction. The heart was enlarged, and there was a loud, harsh systolic murmur and a short diastolic murmur over the aortic area, with absence of the aortic second sound.

The heart weighed 475 Gm and showed hypertrophy and dilatation, especially of the left ventricle. The epicardium of the right ventricle showed marked diffuse fibrosis and opacity. There was slight thickening and vascularity of the aortic leaflet of the mitral valve and focal calcification of the ring of the septal leaflet. Thickening of the anterior tricuspid leaflet and of the anterior and right pulmonary cusps at their commissural insertion was also present.

The aortic valve was bicuspid, consisting of a conjoined left and right coronary cusp and a noncoronary cusp, each measuring 3 cm in length (fig 7 I). Both cusps were appreciably thickened and calcified, especially near the free margin and along the base on their aortic aspects, where there were nodular calcific excrescences partly filling the sinuses of Valsalva.

Commissure A was replaced by an extremely depressed fibrous raphe, measuring 12 by 1 to 3 by 2 to 4 mm, which passed obliquely from the upper level of the sinus of Valsalva to the middle of the aortic aspect of the conjoined cusp. This raphe subdivided the conjoined cusp into equal left and right coronary portions. It was wider and taller in its distal than in its proximal portion, and the outer surface revealed a fissure throughout practically its entire length. The two cusps forming the raphe were not fused symmetrically, there being distinct retraction

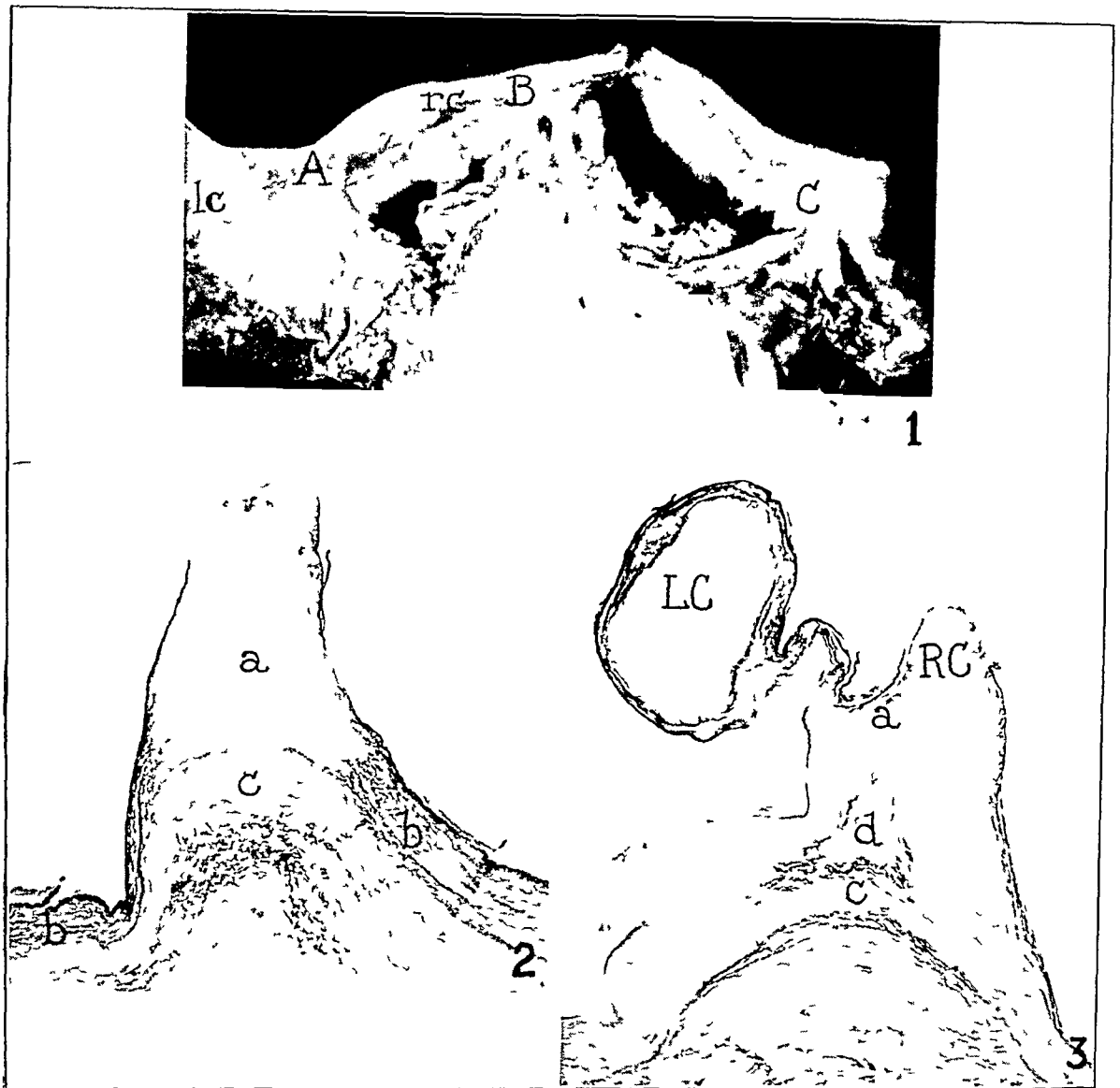


Fig 7—Case 8, a 63 year old white man with calcific sclerosis of an acquired bicuspid aortic valve 1, the raphe at commissure *A* is considerably depressed and reveals a fissure throughout almost its entire extent There is a slight commissural adhesion at *B* 2 transverse microscopic section of the proximal portion of the raphe at commissure *A* The raphe consists of dense, hyalinized connective tissue (*a*) resting on subvalvular endocardium (*c*) and laterally on aortic media (*b*) There is no vascularity or inflammation Weigert elastica stain, $\times 12$ 3, transverse microscopic section of the distal portion of the raphe Note the retraction of the right coronary cusp (*RC*) and the incomplete fusion of the two cusps so that the outermost portion and free margin of the raphe are formed by the left coronary cusp alone (*LC*) At the base of the raphe, just above the subvalvular endocardium (*c*), is a roughly triangular area of fibrosis, vascularity and inflammation containing a number of delicate elastic fibers Weigert elastica stain, $\times 12$

of the right coronary cusp, so that most of the outer portion and free margin of the raphe was formed by the left coronary cusp alone. There was moderate triangular retraction on the ventricular aspect of the conjoined cusp opposite the raphe. Commissure B showed a slight commissural adhesion, while commissure C revealed no change.

Serial transverse microscopic sections of the raphe at commissure A were made. The most proximal portion consisted of a ridge of dense collagenous and hyalinized connective tissue, which was largely acellular and showed areas of atheromatous degeneration in both lateral segments (fig 72). There were also delicate strands of elastic tissue laterally (1 e, in the arterialis layers).

Sections of the middle and distal portions of the raphe showed a similar structure, but there was considerable retraction of the arm of the right coronary cusp toward the valve ring so that the outer segment and free margin of the raphe were formed by the left coronary cusp alone. Along the free margin there were nodular whorls of fibrous tissue and a delicate elastica, while the rest of the raphe showed considerable hyaline and atheromatous degeneration.

The only vascularity present in the raphe occurred distally and in the center of the base, just above the subvalvular endocardium, and was equidistant from the lateral borders (fig 73). The vessels consisted of capillaries and arterioles and were contained in a roughly triangular area of irregular fibrous tissue showing edema, scanty infiltration of lymphocytes and a small number of interlacing elastic fibers.

Sections of the conjoined and noncoronary aortic cusps showed marked nodular calcific deposit, and also ossification, in the ring and in all layers of the free portions. This was accompanied by hyaline and atheromatous degeneration and by considerable vascularization and infiltration of lymphocytes. Sections of the mitral valve revealed diffuse fibrosis, nodular deposit of calcium in the free portion and numerous capillaries in the auricularis layer. The tricuspid valve was also the seat of fibrosis and showed vascularity of the ring and free portion in the spongiosa layer. In the pulmonary valve there was nodular fibrosis of the outer third of the cusp, with no vascularity or inflammation. Other positive findings were calcification, vascularity and inflammation of the intervalvular fibrosa and chronic epicarditis of the right ventricle.

SUMMARY OF EIGHT CASES OF ACQUIRED BICUSPID AORTIC VALVE

The data with respect to age, sex and color and the clinical diagnoses are summarized in the table. This table also shows the character of the lesion of the mitral valve and the other cardiac lesions of rheumatic origin present in each case.

Seven patients were male and 1 was female, and their ages ranged from 13 to 74 years. Seven patients were white and 1 was a Negro. The bicuspid valve was incidental in 3 cases, while in the remaining 5 cases there were clinical diagnoses of valvular disease, namely, aortic stenosis and insufficiency in 2 cases, aortic stenosis in 2 cases and aortic insufficiency in 1 case.

A history of rheumatic fever was obtained in only 1 instance (case 5), that of a 13 year old boy who had severe rheumatic heart disease with mitral stenosis and aortic insufficiency.

Summary of Eight Cases of Acquired Bicuspid Aortic Valve

Case	Age, Yr	Sex	Color	Clinical Diagnosis	Lesions of Aortic Cusps	Mitral Valve		Other Inflammatory Cardiac Lesions (Rheumatic)
						Macroscopic	Microscopic	
1	41	M	White	Endocarditis lenta, mitral stenosis, aortic stenosis and insufficiency	Bacterial endocarditis, calcific sclerosis	Diffuse thickening	Chronic and subacute valvulitis	Chronic tricuspid valvulitis
2	21	M	Negro	Acute appendicitis, diffuse peritonitis	Thickening and inward rolling of free margin of conjoined cusp	Normal	Slight fibrosis	Perivascular scars on myocardium
3	68	M	White	Generalized arteriosclerosis, aortic stenosis and insufficiency, bronchopneumonia	Calcific sclerosis	Diffuse thickening	Focal vascularity, fibrosis	None
4	68	M	White	Carcinoma of kidney, calcific sclerosis of aortic valve with stenosis	Calcific sclerosis	Normal	Focal vascularity, inflammation	Chronic pulmonary valvulitis
5	13	M	White	Rheumatic heart disease with mitral and aortic insufficiency	Acute vegetative endocarditis	Mitral stenosis	Chronic and acute valvulitis	Tricuspid stenosis, acute myocarditis and pericarditis
6	74	M	White	Carcinoma of lung	Calcific sclerosis	Normal	Diffuse vascularity, fibrosis	None
7	49	F	White	Malignant neutropenia	Slight thickening of conjoined cusp	Normal	Diffuse vascularity, fibrosis	Chronic tricuspid valvulitis
8	63	M	White	Calcific sclerosis of the aortic valve with stenosis, hypertension	Calcific sclerosis	Diffuse thickening, focal calcification	Focal vascularity fibrosis	Healed tricuspid and pulmonary valvulitis

Gross Appearance of the Cusps—The acquired bicuspid aortic valve results from complete fusion of two adjoining cusps to form a single conjoined cusp subdivided by a commissural raphe. The lesion differs from the usual commissural adhesion in three respects: (a) The raphe terminates distally well below the line of closure of the conjoined cusp, (b) there is almost complete obliteration of the subvalvular triangular space between the two fused cusps on their ventricular aspect, and (c) the concave sweep of the aortic aspect of the conjoined cusp is uninterrupted along the free margin.

In all cases the conjoined cusp was formed by fusion of the left and right coronary cusps. In 5 cases the conjoined cusp was equal in size to the noncoronary cusp, and in 3 cases it was larger. In 7 cases the conjoined cusp was evenly subdivided by the commissural raphe, while in 1 instance it was subdivided unequally by the raphe into a small left coronary and a larger right coronary segment. Commissures B and C were entirely normal in all but 1 case, in which slight fusion was present at commissure B. Retraction of moderate to considerable degree was present on the ventricular aspect of the conjoined cusp opposite the commissural ridge. In the 2 cases in which no superimposed bacterial or calcific disease existed there was thickening of the conjoined cusp, especially of the free margin adjacent to the raphe.

The Commissural Raphe—The structure was derived from that of two cusps which have undergone inflammatory fusion. Macroscopically, the raphe consisted of a firm ridge of tissue considerably depressed in the sinus of Valsalva and extending obliquely from the upper level of the sinus to a point on the conjoined cusp approximately midway between its base and its free margin. The ridge was of greater height in its distal than in its proximal segment, adjacent to the commissure. In 6 cases the lateral surfaces diverged in the distal portion, which was thus wider than the proximal portion, while in 2 cases the width of the ridge was uniform throughout. The outer surface was smooth and rounded and in 2 cases showed a fissure indicating the line of fusion of the two cusps. This was situated in the middle of the raphe in 1 instance and extended throughout the entire raphe in another. In 2 instances (cases 2 and 8), instead of symmetric fusion of the two cusps forming the raphe, there was retraction of one of the cusps (the right coronary in each case) toward the valve ring, so that a part or all of the outer portion and free margin of the raphe was formed by only one cusp. In 4 of the 5 valves with calcific sclerosis the raphe was also the seat of calcific deposit, especially in the distal portion.

Microscopically the raphe was composed of largely acellular, collagenous and hyalinized connective tissue the base of which rested

proximally on the aortic media and distally on the subvalvular endocardium. No vascularity or inflammation was found in the proximal segment, near the commissure. In every instance, however, vascularization in the form of capillaries and arterioles, irregular fibrosis and inflammation was present distally either in the lower third of the ridge, just above the subvalvular endocardium, or in the middle third, between the ring and the free margin of the cusp. In these regions there were numerous irregularly disposed, delicate elastic fibers. Moreover, the fibrosis and inflammation were usually more prominent toward the central portion of the ridge, i. e., midway between the lateral borders, and hence appeared to involve chiefly the ventricularis layers and the area of organized exudate between them. Although in general the hyalinization of the fused cusps was sufficiently extensive to preclude recognition of individual layers, elastic tissue stains usually revealed remnants of elastica in the arterialis and ventricularis layers. In 2 instances, because of retraction of one of the cusps and incomplete fusion, the two cusps could be identified individually in the outermost portion of the raphe. Distally there was nodular whirling of fibrous tissue to varying degree in the upper third of the ridge and along the free margin, and the fibrous whorls revealed numerous delicate elastic fibers. In the valves with calcific sclerosis the raphe usually showed considerable distortion of architecture, owing to dense, irregular hyaline fibrosis and calcification.

Superimposed Disease of the Valve—In 2 patients the bicuspid lesion was uncomplicated, while the remaining 6 showed superimposed organic disease, namely, 4 had calcific sclerosis, 1 had acute rheumatic valvulitis and 1 had both calcific sclerosis and endocarditis lenta.

Nature of the Mitral Valve—The mitral valve was examined carefully for the presence of chronic or extinct rheumatic disease, and several microscopic sections of both the anterior and the posterior leaflet were made in each case. Macroscopically, the valve was normal in 4 cases, showed diffuse thickening without commissural fusion in 3 cases and was the seat of mitral stenosis in 1 case. Microscopically, however, 2 of the 4 grossly normal valves showed diffuse vascularity and fibrosis, while 1 showed focal vascularity and inflammation. In all, a total of 6 of the 8 mitral valves (cases 1, 3, 5, 6, 7 and 8) revealed conclusive microscopic evidence of healed or active valvulitis, in all probability rheumatic, while 1 (case 4) showed lesions consistent with those of rheumatic disease. Only 1 mitral valve (case 2) showed no vascularity or exudate, although slight fibrosis was present.

Other Rheumatic Lesions Present in the Heart—In 5 cases definite rheumatic lesions were observed elsewhere in the heart than in the

mitral and aortic valves (table) Tricuspid valvulitis was present in 4 cases and pulmonary valvulitis in 2 cases In addition, the perivascular scarring of the myocardium in case 2 may possibly represent healed rheumatic inflammation, since the patient was only 21 years of age and showed no disease of the coronary arteries

COMMENT

Acquired bicuspid aortic valves are to be distinguished from bicuspid valves with fusion of congenital origin The conjoined cusps themselves, with respect to location of fusion, size and general appearance, usually provide no satisfactory means of distinguishing the two lesions This depends on differentiation between a congenital ridge and an acquired commissural raphe

The gross appearance of the congenital ridge is so distinctive as to be virtually pathognomonic³ It consists of a narrow, hemicylindric, barlike elevation of the aorta situated at the commissure, projecting slightly and uniformly into the sinus of Valsalva and directed in the long axis of the aorta The lateral borders are parallel, and the outer surface is smooth and symmetrically rounded with no fissure in the proximal portion The microscopic picture is characteristic⁴ Transverse sections of the proximal portion of the ridge show abundant elastic tissue derived from and continuous with that of the aortic media The elastic laminae pass uninterruptedly across the ridge and are parallel throughout their course, except for the central portion, where there are frequently whorling and irregularity The junction between elastica and annulus fibrosus occurs in the distal segment of the ridge and usually consists of an irregular, inverted V-shaped mass of connective tissue, overlapped both superficially and deeply by the media However, the overlap may be either entirely superficial or entirely deep The elastic fibers extend to a low level in the ridge, often to the attachment of the cusp Blood vessels are scanty, and there is no significant inflammatory or degenerative change

The cause of the acquired bicuspid aortic valve is inflammatory, and in all probability rheumatic The location of the vascularity and inflammation in the commissural raphe, i e, distally and largely in the basal or middle third, indicates that the original fusion of the two cusps occurred within their lateral thirds, just below instead of at the commissure, and

³ Koletsky, S Congenital Bicuspid Aortic Valves, *Arch Int Med*, this issue, p 129

⁴ Lewis, T, and Grant, R T Observations Relating to Subacute Infective Endocarditis, *Heart* 10 21, 1923 Bishop, L F, Jr, and Trubek, M Bicuspid Aortic Valve A Differential Study Between Inflammatory and Congenital Origin, *J Tech Methods* 15 111, 1936 Koletsky³

at a site just above the attachment of the cusps or midway between the ring and the free margin. The result is similar to the rheumatic commissural lesion. In addition, the rheumatic origin is strongly supported by the presence of rheumatic disease in other parts of the heart, notably the mitral valve (table). Seven of the 8 hearts showed conclusive evidence of rheumatic involvement, while in 1 (case 2) there were lesions possibly indicative of rheumatic disease, namely, fibrosis of the mitral valve and perivascular scarring of the myocardium.

In the bicuspid valves with calcific sclerosis, the possibility that the commissural fusions were primarily degenerative (i.e., arteriosclerotic) in origin rather than inflammatory deserves consideration. Against this stands the fact that, except for superimposed calcification, the raphe was entirely similar, macroscopically and microscopically, to those in the noncalcified bicuspid valves. This suggests that the valves were bicuspid before the deposit of calcium. Moreover, all of the hearts with calcific sclerosis showed definite rheumatic involvement of other valves, and this favors a similar origin for the aortic lesion. Although arteriosclerosis cannot be definitely excluded as a cause of the bicuspid aortic valve, it is probably a rare one.

In every instance the bicuspid lesion was formed by fusion of the left and right coronary cusps with the resulting raphe at commissure A (the left coronary-right coronary commissure). In 1 case there was slight fusion at commissure B, while in all the remaining cases commissures B and C showed no change. Should this prove to be the general occurrence, it indicates that such a distribution is necessary to produce the bicuspid valve. Why fusion at commissures B or C does not occur is not clear.

Severe rheumatic heart disease was present in only 1 of the 8 cases, that of a 13 year old boy with mitral and tricuspid stenosis and acute rheumatic pancarditis. In the remaining cases the degree of rheumatic involvement was generally slight, being limited macroscopically to the aortic valve in 3 instances, although rheumatic disease elsewhere, especially in other valves, was demonstrated microscopically. In 1 (case 2), that of a 21 year old man in whom the bicuspid lesion was incidental, the microscopic evidence of disease other than in the aortic valve was equivocal or negative. This bicuspid valve either occurred in a heart with minimal rheumatic involvement elsewhere or represented an instance of isolated rheumatic disease of the aortic valve.

One distinct group of cases of calcific sclerosis of the aortic valve consists of those in which the disease occurs in acquired bicuspid valves. There were 5 such cases in the present study, occurring in persons from 41 to 74 years of age. In all of these cases the calcareous

disease of the aortic valve was the predominant cardiac lesion, while disease of the other valves was minimal or comparatively insignificant. For example, in none of the cases was there any degree of mitral stenosis. In 3 cases there was macroscopic change in other valves, consisting merely of fibrous thickening of the substance of the mitral, tricuspid and pulmonary leaflets. In the remaining 2 cases the other valves were macroscopically normal but chronic or healed inflammatory lesions were demonstrated microscopically.

The evidence indicates that all 5 patients had relatively mild rheumatic heart disease, limited essentially or largely to the aortic valve, which they survived, and on which in later life calcific sclerosis was superimposed. The rheumatic lesion was in all probability the primary predisposing factor in the production of the calcareous disease. In 4 of the 5 cases there was functional disease of the aortic valve, namely, stenosis or insufficiency or both, which was clinically apparent and which led to cardiac decompensation.

The deposit of calcium in such cases occurs gradually, probably over a period of years, and varies in its rate of development and extent with individual predisposition to arteriosclerotic change. Operation of this factor possibly explains the absence of calcification in one of the bicuspid lesions in a woman aged 49 at the time of death.

SUMMARY

Eight cases of acquired bicuspid aortic valve were found in a survey of 3,500 consecutive autopsies. Seven patients were males and 1 was female, and their ages ranged from 13 to 74 years. In all cases the bicuspid lesion resulted from complete fusion of the left and right coronary cusps, producing a raphe at commissure A (the left coronary-right coronary commissure), while commissures B and C were usually essentially normal. The lesion was uncomplicated in 2 cases, while in 6 cases there was superimposed organic disease, namely, 4 had calcific sclerosis, 1 had acute rheumatic valvulitis and 1 had both calcific sclerosis and endocarditis lenta.

The commissural raphe consisted of a firm ridge of tissue, considerably depressed in the sinus of Valsalva, directed obliquely in the sinus, of greater height and usually of greater width distally than proximally and with a rounded outer surface which occasionally revealed a fissure indicating the line of fusion of the two cusps. Microscopically, the raphe was composed essentially of hyalinized connective tissue the base of which rested proximally on aortic media and distally on the subvalvular endocardium. Vascularity and inflammation were limited to the distal

portion and were usually situated in the lower or the middle third of the ridge, between the ring and the free margin of the cusp

The fusion of the leaflets was evidently due to inflammation, probably rheumatic in origin. The structure of the raphe corresponded to that of the usual rheumatic commissural lesion, and in 7 of the 8 cases rheumatic lesions were demonstrated in other parts of the heart. However, the degree of rheumatic involvement was generally slight, being limited essentially or largely to the aortic valve. Patients usually survive such relatively mild rheumatic heart disease and are then predisposed in later life to the development of superimposed calcific sclerosis of the aortic valve.

HYPERACTIVE CARDIOINHIBITORY CAROTID SINUS REFLEX

A POSSIBLE AID IN THE DIAGNOSIS OF CORONARY DISEASE

LOUIS H SIGLER, M D

BROOKLYN

Within the past few years, since the publication of the comprehensive experimental work on the carotid sinus reflex by Hering¹ and Heymans,² there has been some application of the knowledge regarding this reflex to clinical medicine. The most important contributions are those of Weiss and Baker,³ Ferris, Capps and Weiss⁴ and Weiss, Capps and Ferris⁵. They showed the relation of a hyperactive reflex to some of the unconscious and convulsive states in man.

That unconsciousness and convulsions might be induced in some persons by pressing on a carotid artery at its bifurcation has been known for hundreds of years. Ask-Upmark⁶ stated that the Assyrians used this method to dull pain during the rites of circumcision. The mechanism of its production, however, was not known until of late.

Before the hyperactive cardioinhibitory carotid sinus reflex is considered, the normal carotid sinus mechanism with its various reflex responses must be clearly understood.

The normal mechanism is a protective adaptation to help maintain normal circulation, respiration and other activities of the body. It consists of a set of nervous structures whose main receptor organs are located where the internal carotid artery pouches out at its junction with the external carotid artery. The nerve fibers emerging from these receptor organs form the sinus nerve, which joins the glossopharyngeal nerve,

1 Hering, H. E. *Karotissinusreflexe auf Herz und Gefasse*, Dresden, Theodor Steinkopff, 1927.

2 Heymans, C. *Le sinus carotidien et les autres zones vasosensibles réflexogènes*, London, H. K. Lewis and Co., 1929.

3 Weiss, S., and Baker, J. P. The Carotid Sinus Reflex in Health and Disease. Its Rôle in Causation of Fainting and Convulsions, *Medicine* **12** 298, 1933.

4 Ferris, E. B., Capps, R. B., and Weiss, S. Carotid Sinus Syncope and Its Bearing on the Mechanism of the Unconscious State and Convulsions, *Medicine* **14** 377, 1935.

5 Weiss, S., Capps, R. B., and Ferris, E. B. Syncope and Convulsions Due to a Hyperactive Carotid Sinus Reflex, *Arch. Int. Med.* **58** 407 (Sept.) 1936.

6 Ask-Upmark, E. The Carotid Sinus and the Cerebral Circulation, *Acta psychiat. et neurol.*, 1935, supp. 6, p. 1.

running to the medulla. This nerve tract carries the main afferent pathways which convey the nerve impulses originating in the sinus region to the medullary centers in the brain. According to Brauecker,⁷ afferent tracts are also located in the vagus nerve, the sympathetic system and the hypoglossal nerves, and the origins of such tracts are not confined to the carotid sinus but are found also in the common carotid artery at its bifurcation and in the adjoining part of the external carotid artery. Entering the medulla, the afferent tracts make synoptic connections at the various centers with the motor or efferent pathways, which terminate in various organs of the body. Figure 1 is a diagrammatic representation

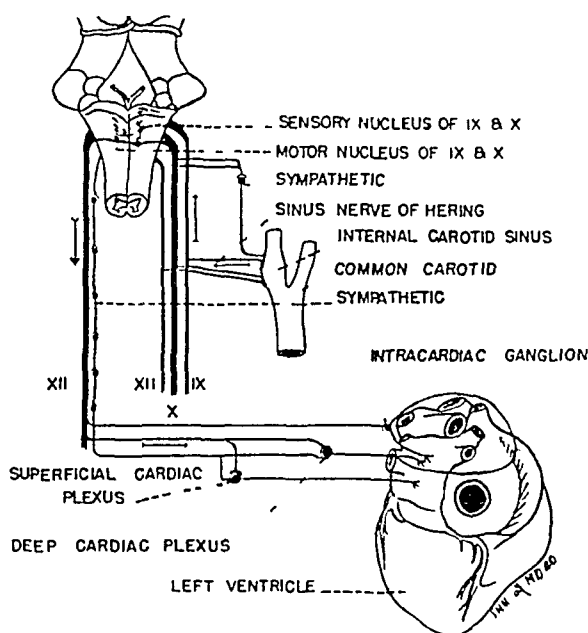


Fig 1—Diagram of the cardioinhibitory carotid sinus reflex tracts. The carotid sinus, the afferent nerves, the medullary centers, the efferent tracts, the cardiac ganglionic connections and their terminations in the different parts of the auricles are schematically represented (see text)

Under normal conditions, the stimulus which produces the various reflexes consists of changes in arterial blood pressure. Sudden spontaneous increase in blood pressure stimulates the receptor organs and sets up afferent impulses which enter the various medullary centers and result in vasodepression, cardioinhibition, some alteration in respiration and decreased epinephrine secretion, all of which have a tendency to return the blood pressure to normal. A sudden drop in pressure in the carotid arteries produces reflexes having the opposite effects.

The sinus nerves possess natural tonus tending to help maintain the blood pressure and cardiac rate at certain levels. This is evidenced by the

⁷ Brauecker, W. Das pressorezeptorische Nervensystem und seine praktische Bedeutung in der Chirurgie, Beitr z klin Chir **158** 309, 1933

fact that if both nerves are cut some rise in pressure and acceleration of the heart will result. The two sinus nerves, together with the two aortic depressor nerves, constitute the four bridles of the circulation. In both cases hydrodynamic changes of the circulation constitute the adequate stimulus.

In some persons and in certain diseased states, the carotid sinus mechanism becomes hyperactive. In such cases, external stimulation, such as the application of external pressure in the region of the carotid sinus, may result in a great exaggeration of the various responses. There may develop an extreme and dangerous drop in blood pressure, an appreciable slowing or stoppage of the heart and distinct cerebral manifestations. It is noteworthy that various persons show different kinds and degrees of exaggerated response. In some cases, slowing or stoppage of the heart occurs. In others, a more or less noticeable fall in blood pressure takes place. In still others, cerebral or respiratory manifestations are outstanding. These may occur singly or in various degrees of combination. The variation in response is undoubtedly due to hyperirritability of the different centers and of the responsive organs, as will be discussed later.

In the last few years I have become interested in the hyperactive cardioinhibitory reflex of the abnormal carotid sinus group of responses. I found that this reflex, if it occurs at all, usually appears before and often commences to subside at a time when the other reflexes reach their highest effects. I also observed⁸ that the reflex occurs with much greater frequency and to higher degrees in males, in advanced age and in the presence of demonstrable coronary disease. It was therefore felt that the test might perhaps be used as an aid in the diagnosis of coronary disease. To evaluate it as such, a larger number and variety of cases were necessary for comparative study. I have accordingly analyzed the records of 1,886 additional patients on whom the test was performed as a routine. This report covers that series of patients.

MATERIAL AND METHOD OF STUDY

The series consisted of 1,151 males and 735 females, whose ages ranged between 10 and 85 years. The majority were ambulatory, office patients. The test was performed with the patient in the sitting position, if ambulatory, or in the recumbent position, if bedridden. In the sitting position, the response was usually quicker and was more pronounced. The head was extended, and the carotid arteries at the level

8 Sigler, L. H. Clinical Observations on the Carotid Sinus Reflex. I. The Frequency and the Degree of Response to Carotid Sinus Pressure Under Various Disease States, *Am J M Sc* **186** 110, 1933, Clinical Observations on the Carotid Sinus Reflex. II. The Response to Carotid Sinus Pressure at Various Ages and Heart Rates and Rhythms, *ibid* **186** 118, 1933, Further Observations on the Carotid Sinus Reflex, *Ann Int Med* **9** 1380, 1936.

of the cricoid cartilage were located and were gradually compressed against the spinous processes while the examiner listened to the heart. It is essential that pressure be exerted slowly and with progressively greater force, for in extremely hypersensitive persons the slightest amount of pressure may bring about alarming symptoms and complete and prolonged stoppage of the heart. The test should be done on one side of the neck at a time for the same reason. The cardiac rate obtained before the pressure test was then compared with that following the maximum amount of compression, and the percentage of slowing was calculated.

The cases were divided into four main groups, as follows: group I, persons with various grades of demonstrable coronary sclerosis, with or without hypertension or other diseased states; group II, persons with hypertension, with or without evidence of arteriosclerosis or other diseased states, but without demonstrable evidence

TABLE 1—*Incidence and Degrees of Hyperactivity of the Carotid Sinus Reflex in Various Age Groups for Males (M) and Females (F) **

Ages	Sex	Incidence of Response			Degrees of Response							
		Total Sub jects	No Resp		+		++		+++		++++	
			No Resp	% Resp	No Resp	% Resp	No Resp	% Resp	No Resp	% Resp	No Resp	% Resp
Less than 20	M	51	16	31.4	8	50.0	5	31.2	3	18.8	0	0.0
	F	36	20	55.6	11	55.0	9	45.0	0	0.0	0	0.0
21 to 30	M	81	31	28.3	8	25.8	13	41.9	8	25.8	2	6.5
	F	109	53	48.7	18	33.9	20	37.7	13	24.5	2	3.9
31 to 40	M	170	138	81.2	37	26.8	45	32.6	29	21.0	27	19.6
	F	117	74	63.3	19	25.6	54	45.9	19	25.6	2	2.9
41 to 50	M	340	308	90.6	52	16.8	89	28.8	82	26.6	85	27.8
	F	168	107	63.7	30	28.0	46	42.9	18	16.8	13	12.3
51 to 60	M	347	312	90.0	45	14.4	81	25.9	71	22.9	115	36.8
	F	191	139	72.8	35	25.1	47	33.8	34	24.4	23	16.7
Over 60	M	162	141	87.0	11	7.8	30	21.2	38	26.9	62	44.1
	F	114	77	67.5	25	32.4	27	35.0	12	15.5	13	17.1

* The ages are given in years. The number of persons examined in each group is shown under "Total Subjects", the number that responded under "No Resp" and the calculated percentage responding under "% Resp". The degrees of response are designated by plus marks, and under each degree are shown the number responding and the percentage response for each group: +, less than 10 per cent slowing of the heart; ++, 10 to 30 per cent slowing of the heart; +++, 30 to 70 per cent slowing of the heart; +++, stoppage of heart for three seconds or more.

of coronary sclerosis, group III, persons with cardiac disease other than the arteriosclerotic type, and group IV, normal persons and persons presenting constitutional disease with no hypertension or demonstrable cardiac disease.

The degrees of cardioinhibition in each group were designated by plus marks as follows: 1 plus, if the slowing was less than 10 per cent, 2 plus, if there was 10 to 30 per cent slowing, 3 plus, if the slowing was 30 to 70 per cent, and 4 plus, if the heart stopped for at least three seconds.

The incidence and the degrees of response in the various age groups in this series are shown in table 1 and figures 2 and 3.

The percentage in the incidence of response among males suddenly rises after the age of 30 and reaches a maximum after 40. In females the incidence is smaller at all ages with an abrupt rise after 30, but the peak is not reached until after 50. The reason for the comparatively high incidence of response in the age group of less than 20 years is probably the frequent presence of rheumatic or congenital cardiac disease in this age group.

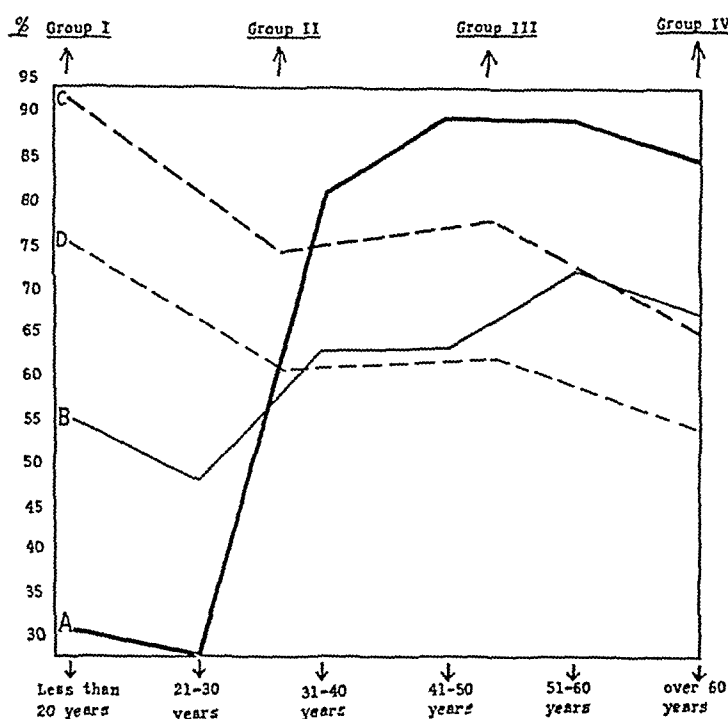


Fig 2—Incidence of response to carotid sinus pressure at various ages and in various groups of diseases, expressed in percentage of cases *A*, age groups, males, *B*, age groups, females, *C*, disease groups, males, *D*, disease groups, females Group I, coronary disease, group II, hypertensive disease, group III, cardiac disease other than coronary, group IV, no cardiac or hypertensive disease

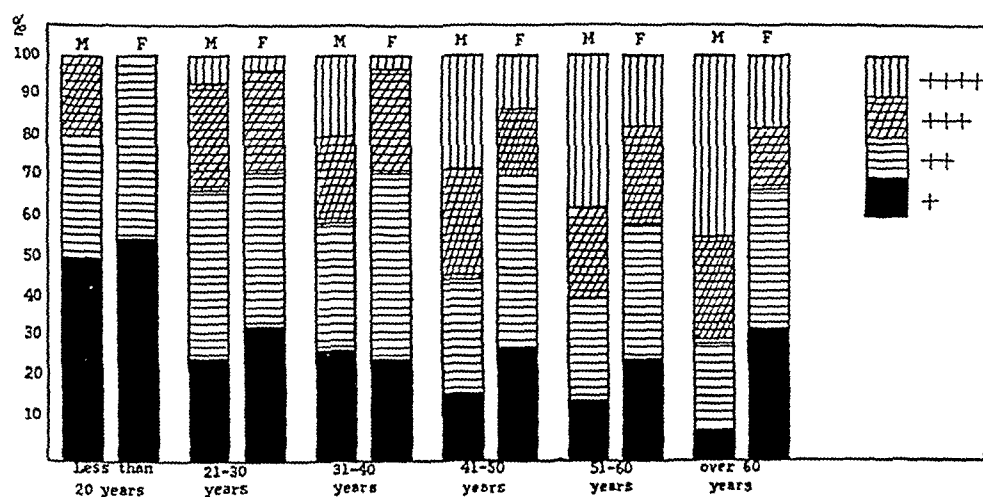


Fig 3—The relative number of persons with various degrees of response to carotid sinus pressure in each age group, expressed in percentages for males (*M*) and females (*F*) +, less than 10 per cent slowing of the heart, ++, 10 to 30 per cent slowing of the heart, +++, 30 to 70 per cent slowing of the heart, ++++, stoppage of heart for three seconds or more

The degree of response is also proportional to advance in age, both in males and females, but it is lower in females

The incidence and the degrees of response in the various disease groups are shown in table 2 and figures 2 and 4. It will be seen that the coronary disease has the highest incidence, with 92.6 per cent of the males and 76 per cent of the females responding. The other cardiac disease group comes next, the hypertensive group, third, and the general constitutional disease group, last. Females show a lower incidence in all groups. The degrees of response are in approximately the same order of frequency in the various groups, and the same difference exists between males and females. In the hypertensive group, a smaller number of patients show the higher degrees of response than in any other group.

RESPONSE IN VARIOUS GRADES OF CORONARY DISEASE

If the presence of coronary disease is one of the causes of a hyperactive reflex, the frequency and the degrees of response should corre-

TABLE 2—*Incidence and Degrees of Response in the Various Disease Groups**

Groups	Sex	Incidence of Response			Degrees of Response							
		Total Subj	Response		+		++		+++		++++	
			No Resp	% Resp	No Resp	% Resp	No Resp	% Resp	No Resp	% Resp	No Resp	% Resp
I	M	638	591	92.6	70	11.8	128	21.6	160	27.0	233	39.6
	F	230	175	76.0	41	23.3	51	29.0	46	26.6	37	21.1
II	M	96	72	75.0	14	19.4	34	47.2	16	22.2	8	11.2
	F	170	105	61.7	33	31.4	51	48.5	17	16.1	4	4.0
III	M	71	56	78.8	15	26.7	16	28.5	14	25.0	11	19.8
	F	81	51	62.9	20	39.2	20	39.2	10	19.6	1	2.0
IV	M	346	227	65.6	62	27.3	85	37.4	41	18.0	39	17.3
	F	254	139	54.7	44	31.6	61	43.8	23	16.6	11	8.0

* Group I, coronary disease, group II, hypertensive disease, group III, cardiac disease other than coronary, group IV, no cardiac or hypertensive disease. The designation of the columns is the same as in table 1.

spond to the extent of such disease. There should be less tendency for the response to occur in the mild than in the more advanced grades. To determine that, the coronary disease group was subdivided into three series of persons with a mild, moderate or severe grade of disease, and the relative incidence and the degrees of response in each series were analyzed.

It must be emphasized that this analysis was based entirely on the clinical and electrocardiographic manifestations of the disease, which evidences are known to present extreme variability and are, therefore, possible sources of error. This possibility was diminished greatly by carefully following the accepted criteria for the diagnosis of coronary disease and by observing most of the cases for a period of one to six years.

In the series with a mild grade of disease were placed persons presenting epigastric or precordial oppression, discomfort, pain or dyspnea

coming on after considerable exertion and abating after exertion was stopped. The physical examination either gave negative results or showed slight cardiac enlargement and slight changes in the intensity and the character of the first sound. The blood pressure was either normal or elevated. The electrocardiogram, likewise, was either normal or showed slight deviations from the normal, such as rounding of the QRS-T segment in one or more leads with or without slight depression or elevation, slight slurring or notching of the QRS complex in two leads, diminished voltage of the QRS complex and slight abnormalities of the T wave. In many of these cases the diagnosis was established later, after the occurrence of an acute episode of coronary thrombosis or the development of more characteristic symptoms and signs.

A typical example is that of a man 42 years old, first seen on March 23, 1938, when he complained of weakness in the legs of two weeks'

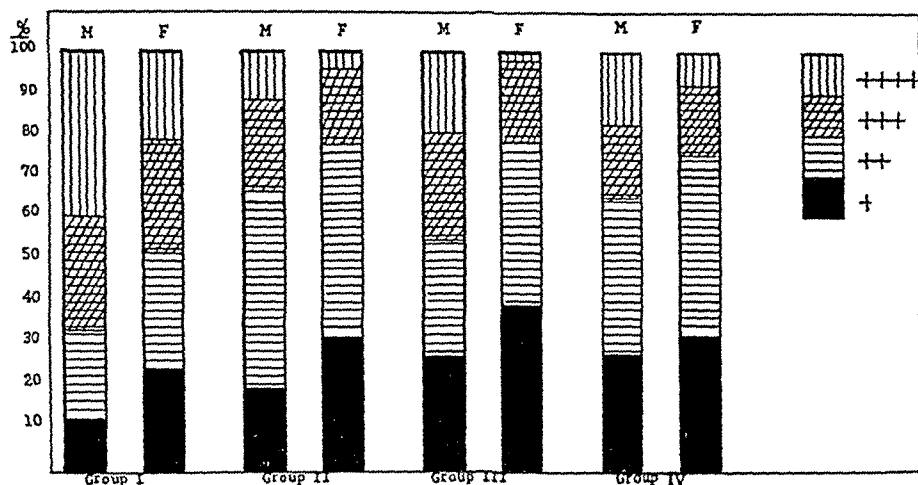


Fig 4—The relative number of persons with various degrees of response to carotid sinus pressure in each disease group, expressed in percentages for males (M) and females (F). Group I, coronary disease, group II, hypertensive disease, group III, cardiac disease other than coronary, group IV, no cardiac or hypertensive disease. The degrees of response are expressed in plus marks as in figure 3.

duration, precordial pain on the left side and slight dyspnea after walking up three flights of stairs. He could walk fifteen blocks with only slight dyspnea and no pain.

On physical examination, the heart was found to be of normal size and shape, and the rate and rhythm were normal. There was slight diminution in the intensity of the first sound. The lungs were normal. The palpable vessels were normal, and the blood pressure was 126 systolic and 86 diastolic. The electrocardiogram (fig 5A) was practically normal, except for slight rounding of the RT segment in the first and second leads. Pressure on the right or left carotid sinus yielded a 2 plus response. He was considered to have mild coronary disease.

mainly because of the subjective symptoms. On July 19, 1939, about fifteen months after the first examination, an acute coronary occlusion developed. An electrocardiogram obtained six days after the attack (fig 5 *B*) corroborated the clinical diagnosis of occlusion. It was interesting to find that compression of the carotid sinus at this time gave a 3 plus response.

In the series with a moderate grade of disease were placed persons who presented considerable dyspnea, precordial pain, tightness and dis-

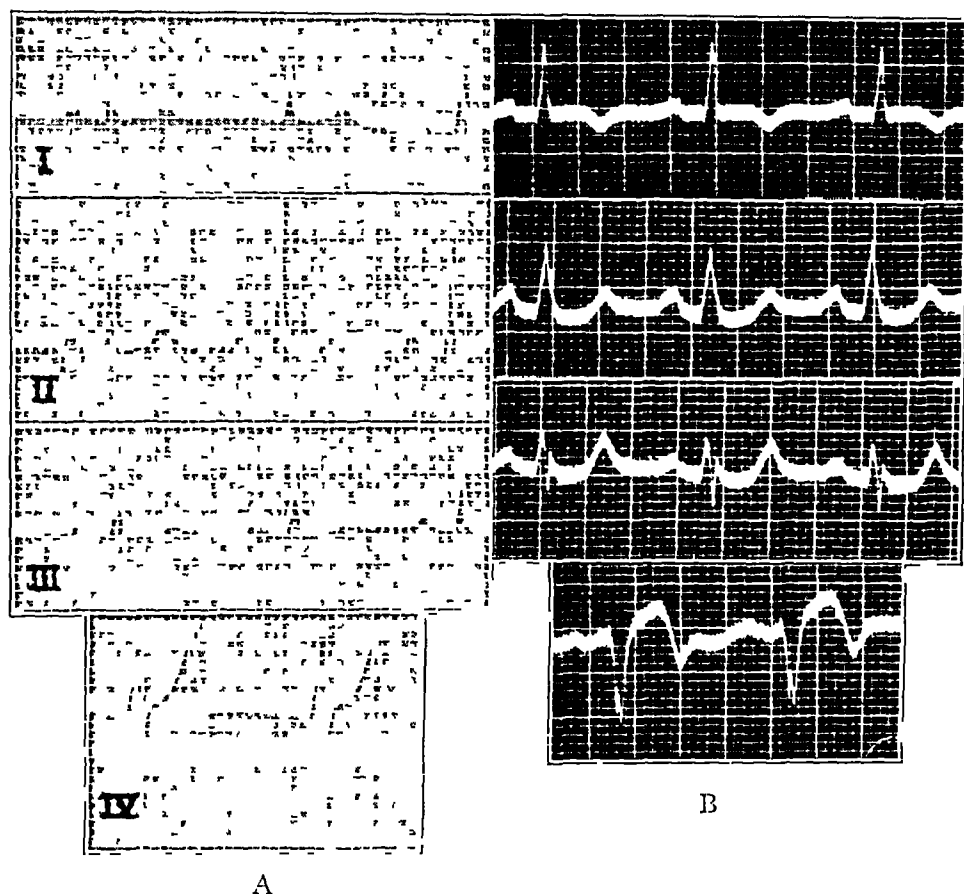


Fig 5—*A*, March 23, 1938, tracing essentially normal except for slight rounding of the RT segment in the first and second leads. *B*, July 25, 1939, gross changes in all the complexes, including those of the fourth lead.

comfort, with or without typical radiation, coming on after relatively slight exertion, such as walking three or four blocks or up one flight of stairs. Many of these patients complained of other disturbances, such as "heartburn," "indigestion," pressure in the epigastrium, dizziness, pulling sensations in one or both arms, retrosternal viselike compression, "gaseous pressure" and weakness. The physical findings were normal in many cases, and in these the diagnosis was based on the history and subsequent course. Most patients, however, showed more or less cardiac enlargement, aortic sclerosis and some peripheral arteriosclerosis, with or

without hypertension. The first heart sound was split, muffled or diminished in intensity, and an occasional faint systolic murmur was heard at the apex. The electrocardiogram was normal in some. In others there were slight or moderate deviations from the normal, such as prolongation of the interventricular conduction time to 0.12 seconds, slurring and notching of the QRS complex, depression or elevation of the QRS-T segment with or without rounding, the presence of a large Q wave in the third lead and an isoelectric or negative T wave in two leads.

In the series with a severe grade of disease were placed persons who had one or more episodes of coronary occlusion and who showed the anginal syndrome or congestive failure to a great degree. Many of these had frequent attacks of nocturnal dyspnea and were subject to angina and dyspnea on the slightest exertion. Although the electro-

TABLE 3—*Incidence and Degrees of Response in the Various Grades of Coronary Disease, With or Without Hypertension**

Grades of Coronary Disease	Sex	Incidence of Response			Degrees of Response							
		Total Sub- jects	No Resp		+		++		+++		----	
			No Resp	% Resp	No Resp	% Resp	No Resp	% Resp	No Resp	% Resp	No Resp	% Resp
Mild	M	123	105	85.3	31	29.5	29	27.6	22	21.0	23	21.9
	F	88	57	64.7	26	45.6	14	24.5	11	19.3	6	10.6
Moderate	M	264	250	94.7	27	10.8	57	22.8	82	32.8	84	33.6
	F	73	59	80.8	7	11.8	21	35.6	15	25.4	16	27.2
Severe	M	251	236	94.0	17	7.2	47	20.0	54	22.8	115	50.0
	F	69	59	85.5	8	13.5	17	28.8	19	32.2	15	25.5

* The designation of the columns is the same as in table 1.

cardiogram was normal in some, most of the patients displayed an appreciable defect in intraventricular conduction, bundle branch block, auricular fibrillation, or one of various other disturbances in rhythm, such as marked T wave changes in the conventional, as well as in the precordial, leads and QRS-T segment changes. The physical examination showed more or less cardiac enlargement, although in some the size of the heart was normal. There were usually distinct changes in the character and intensity of the first sound. Gallop rhythm was frequently observed. There was usually considerable peripheral vascular sclerosis, and hypertension was often noted. The lungs frequently showed more or less congestion, and peripheral edema, as well as enlargement of the liver, was occasionally seen.

The cardioinhibitory response to carotid sinus stimulation in the various grades of coronary disease is shown in table 3 and figures 6 and 7. It will be seen that both the incidence and the degrees of response have some relationship to the degree of coronary disease. In the cases of mild grades of coronary disease fewer patients respond and the lower

degrees of response predominate As the severity of coronary disease increases, both the incidence and the degrees of response become greater

RESPONSE IN THE GROUP WITH GENERAL CONSTITUTIONAL DISEASES

To determine the extent of cardioinhibition associated with various diseased states other than cardiac disease or hypertension, group IV was

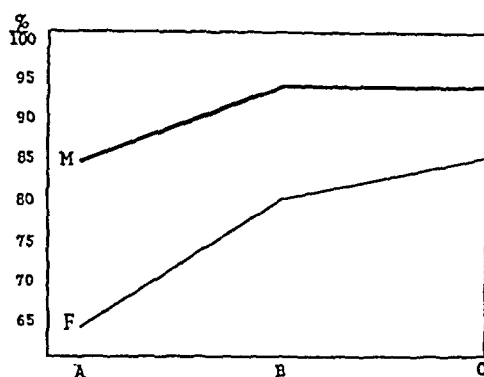


Fig 6—Incidence of response in various grades of coronary disease, expressed in relative percentage of cases for males (*M*) and females (*F*) *A*, mild, *B*, moderate, *C*, severe

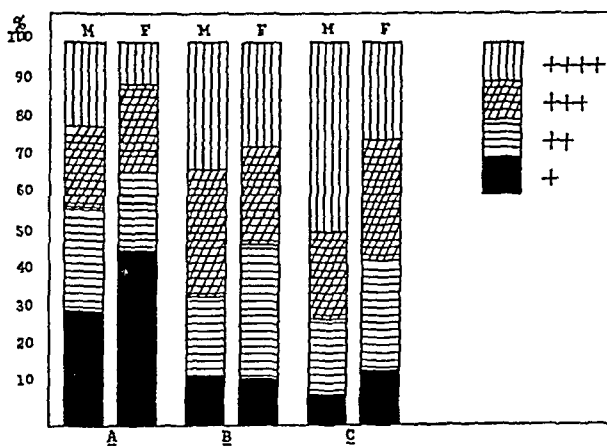


Fig 7—Degrees of response in various grades of coronary disease expressed in relative percentage of cases for males (*M*) and females (*F*) *A*, mild, *B*, moderate, *C*, severe The degrees of response are expressed in plus marks as in figure 3

subdivided into four subgroups In the first were placed persons having no disease, in the second, persons presenting various forms of neuroses, in the third, persons having various grades of arteriosclerosis with or without other disease and in the fourth, persons having miscellaneous constitutional diseases The relative incidence and the degrees of

response in each subgroup are shown in table 4 and figures 8 and 9. It will be seen that the subgroup with no disease has the lowest incidence and degrees of response. In the arteriosclerotic subgroup, the incidence and the degrees of response are very high, approaching closely those of the coronary disease group. This may be due to the presence in this subgroup of unrecognized coronary disease. As there were only two females in this group, the figures for females cannot be considered of any significance. The subgroup with miscellaneous diseases shows intermediate figures. This subgroup consisted of patients with the following diagnoses: obesity and other nutritional disturbances, Frohlich's syndrome, Hodgkin's disease, chronic bronchitis and emphysema, duodenal ulcer, cirrhosis of the liver, Henoch's purpura, acute rheumatic fever, cholelithiasis and cholecystitis, thyrotoxicosis, leukemia, diabetes

TABLE 4—*Incidence and Degrees of Response in the Various Subgroups of the Group of Patients Without Cardiac Disease*

Diagnosis	Sex	Incidence of Response			Degrees of Response							
		No Sub jects	No Resp	% Resp	+		++		+++		++++	
					No Resp	% Resp	No Resp	% Resp	No Resp	% Resp	No Resp	% Resp
No disease	M	84	32	38.0	18	50.2	9	28.1	3	9.3	2	6.4
	F	41	13	31.7	8	61.5	3	23.0	2	15.5	0	0.0
Neurosis	M	120	79	65.8	23	29.2	32	40.5	19	24.0	5	6.3
	F	132	74	56.0	20	27.0	37	50.0	12	16.2	5	6.8
Arteriosclerosis	M	59	52	88.1	4	7.6	18	34.6	10	19.2	20	38.6
	F	2	1	50.0	1	100.0	0	0.0	0	0.0	0	0.0
Miscellaneous *	M	83	64	77.1	20	31.2	24	37.5	8	12.6	12	18.7
	F	89	61	68.5	15	24.5	31	50.8	9	14.7	6	10.0

* For the various diseased states in the "Miscellaneous" subgroup, refer to the text.

mellitus, allergy, pulmonary tuberculosis, pancreatic and gastrointestinal malignant growths, nephrolithiasis, cerebral tumor, chronic arthritis, nephritis, multiple sclerosis, pulmonary embolization, menopause, epilepsy, syphilis, bronchial asthma, mediastinal tumor, bronchogenic carcinoma, pyelitis, colitis, and pituitary disturbances. It must be emphasized here that many of these patients were of the arteriosclerotic age and had evidence of arteriosclerosis in addition to the other diagnosis.

COMMENT

The analysis of the cases of this series of 1,886 patients shows that a hyperactive cardioinhibitory carotid sinus reflex occurs with much greater frequency in coronary disease than in any other condition. Compared with the normal group, the frequency is about 50 per cent greater in persons with coronary disease, compared with persons with other diseased states, it is about 30 per cent. In females, the difference is smaller. This may be due partly to the fact that the incidence of

coronary disease in females is much smaller. Coronary disease also yields a greater number of cases with higher degrees of response, and the more advanced the disease, the greater is the incidence and the higher are the degrees of response. Heart disease other than the arteriosclerotic

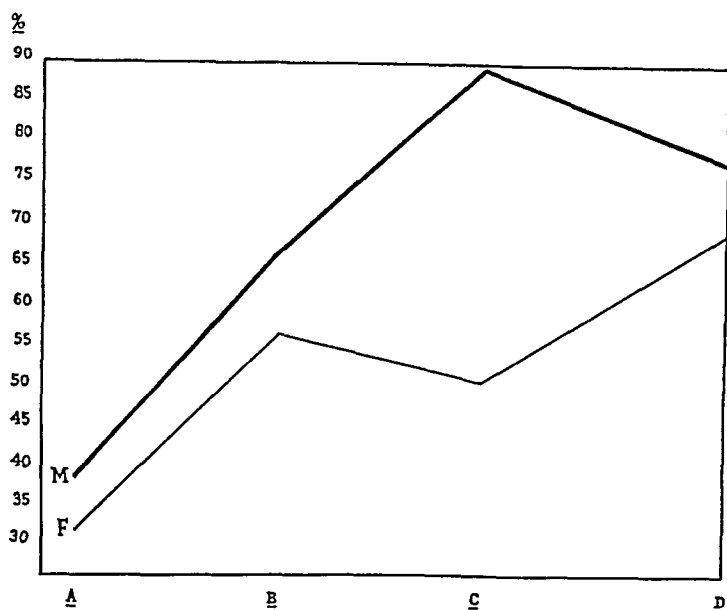


Fig 8—Incidence of response in the group without cardiac disease expressed in percentage of cases for males (*M*) and females (*F*) *A*, normal persons, *B*, persons with various neuroses, *C*, persons with arteriosclerosis, *D*, persons with miscellaneous diseases (see text)

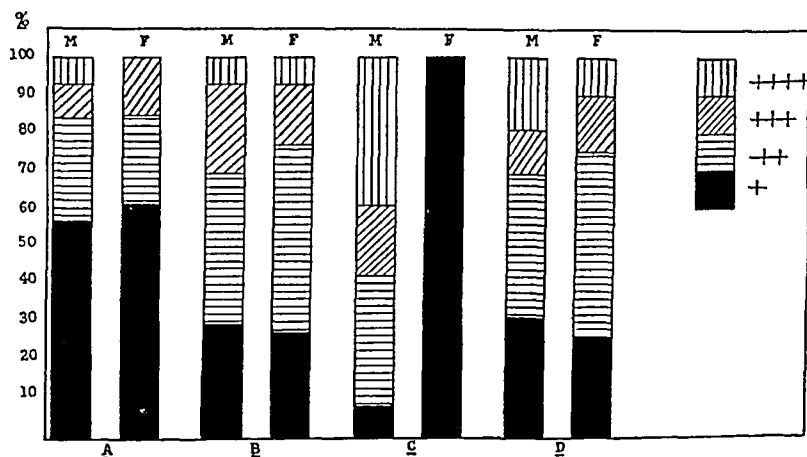


Fig 9—Degrees of response in the group without cardiac disease, expressed in relative percentages of cases for males (*M*) and females (*F*) *A*, normal persons, *B*, persons with various neuroses, *C*, persons with arteriosclerosis, *D*, persons with miscellaneous diseases (see text)

type also shows a slightly greater incidence and higher degree of response than the other conditions, even though such disease in my series occurred in young persons, in whom normally the response is rare

The comparative frequency of a hyperactive cardioinhibitory reflex in persons with conditions other than heart disease and even in normal persons, however, eliminates such disease as the only possible cause of the condition

On considering 1 plus and 2 plus responses as being perhaps non-pathologic and confining attention to the higher degrees of response, which are definitely abnormal, it becomes necessary to find a physiologic basis for such hyperactivity. This is to be sought either in excessive sensitivity of the carotid sinus region or in hyperirritability of the cardioinhibitory center or in some alterations of the vagal ganglionic connections in and near the heart. If hyperactivity is due to the first two conditions, coronary or other heart disease cannot be blamed for the hyperactive reflex. If, on the other hand, local changes in the heart ganglions are also responsible, it may explain the more frequent occurrence of the hyperactive state in coronary disease.

That local hypersensitivity of the carotid sinus receptor organs plays a part is a possibility which has never been proved. Heimg,¹ Koch,⁹ and Heymans² attributed a hyperactive reflex in occasional cases of local sclerotic changes in the internal carotid artery. Keele,¹⁰ however, found no such relationship in 55 cases at autopsy. The frequent absence of local sclerosis in patients with a hyperactive reflex and the presence of the sclerosis in the absence of the reflex corroborate Keele's observations. Also, the fact that various persons show different types and degrees of reflex response under the same type of stimulation tends to eliminate local hypersensitivity of the carotid sinus region as a cause. The carotid sinus must be considered merely a region, with receptor organs and afferent connections with the bulbar centers, which easily picks up and conveys impulses to such centers. The response to these impulses depends either on the sensitivity of the centers or on the condition of the end organs on which the efferent impulses play, or on both. This assumption is further substantiated by the fact that the same type of cardioinhibition which is characterized by slowing and arrest of the sinus and by disturbances in sinoauricular and auriculoventricular conduction and which is seen in the hyperactive cardioinhibitory reflex, as described in a previous communication,¹¹ has also been obtained by stimulation of other parts of the body having afferent tracts leading to the cardioinhibitory center. Examples are the oculocardiac reflex and

9 Koch, E. Ueber dem depressorischen Gefassreflex beim Karotisdruckersuch an Menschen, *Munchen med Wehnschr* **71** 704, 1924

10 Keele, C. A. Pathological Changes in Carotid Sinus and Their Relation to Hypertension, *Quart J Med* **2** 213, 1933

11 Sigler, L. H. Electrocardiographic Observations on the Carotid Sinus Reflex, *Am Heart J* **9** 782, 1934

the swallowing and respiratory reflexes, as well as impulses coming from stimulation of many sensory nerves, as described by Fogelson¹²

By hyperirritability of the center or of the terminal ganglionic connections in or near the heart I mean alterations in the synapses in these areas which make the synapses more capable of transmitting impulses. The synapse is a specialized structure separating one neuron from the other by a definite membrane. According to Macleod,¹³ this structure has a dual function. It acts as a valve in preventing impulses from passing back in the opposite direction, and it *offers resistance* to the passage of an impulse from the receptor to the effector organs. The myoneurial junction also acts as a synapse in that respect.

Under normal conditions the synaptic resistance prevents the passage of impulses with force sufficient to produce deleterious effects. Under abnormal conditions the resistance either is increased, resulting in insufficient response to normal environmental states, or is greatly lowered or abolished entirely, resulting in an exaggerated or pathologic response.

The fact that the heart is provided with an unusually large local system of neurons and synapses demonstrates the natural protective adaptation of that organ. The special set of neurons and multiple ganglionic connections are located in the superficial and deep cardiac plexuses and in the cardiac ganglions. In the former, both the sympathetic system and the vagus nerve make synaptic connections. In the cardiac ganglions, on the other hand, according to Woollard¹⁴ and Lawrentjew,¹⁵ only vagal nerve fibers make such connections. These ganglions are found in abundance in the subepicardial connective tissue on the anterior and posterior surfaces of the auricles, especially the left auricle, the interauricular septum and the auriculoventricular sulcus. They are thus situated in an area of the heart very close to the sinoauricular and auriculoventricular conduction apparatus, which initiate and propagate the normal cardiac impulse. They undoubtedly stand guard against the sudden overwhelming of this apparatus by vagal inhibition.

In pathologic states, especially those caused by nutritional disturbances, it is conceivable that the normal resistance offered at these

12 Fogelson, L. J. Die Wirkung der extracardialen Nerven auf das Herz, vor und nach der Ausschaltung des Sinusknoten, *Ztschr f d ges exper Med* **68** 145, 1929.

13 Macleod, J. J. R. *Physiology and Biochemistry in Modern Medicine*, ed 5, St. Louis, C. V. Mosby Company, 1927.

14 Woollard, H. H. The Innervation of the Heart, *J. Anat.* **60** 345, 1926.

15 Lawrentjew, H. J. Experimentell-morphologische Studien über den feineren Bau des autonomen Nervensystems. I. Die Beteiligung des Vagus an der Herznervation, *Ztschr f mikr-anat Forsch* **16** 383, 1929.

ganglions, as well as at the ganglions of the cardiac plexuses, is greatly diminished or is lost entirely. The sudden onslaught of the vagal efferent impulses induced by carotid sinus stimulation is, then, uninterruptedly transmitted to the heart and results in the abnormal response.

That cardioinhibition is accentuated by lessening the coronary blood supply to the heart was demonstrated experimentally by Suschtschinsky¹⁶ as long ago as 1868. In the literature there are clinical records of many cases of marked vagal disturbances of the heart, induced by various reflexes, such as swallowing. In many instances cardiac damage due to coronary disease was found on postmortem examination. The case reported by Starling¹⁷ is of particular interest. The patient had recurring attacks of unconsciousness due to stoppages of the heart induced by swallowing. These were abolished by atropine. Gross pathologic changes in the conduction apparatus were observed at autopsy. Starling interpreted the attacks as being due to vagal impulses which played on a highly diseased structure and yielded an unphysiologic response.

The association of a hyperactive cardioinhibitory carotid sinus reflex with arteriosclerosis and coronary disease was observed as long ago as 1799 by Parry¹⁸ and many years later by Concoto,¹⁹ de Cereville,²⁰ Wenckebach,²¹ Daniélopou and Missirlin,²² Braun and Samet²³ and others. Their reports concerned isolated cases, and they thought that the condition was caused by direct stimulation of the vagus nerve in the neck.

That constitutional and toxic states of the body, in addition to local pathologic changes, may make the heart unduly responsive to vagal effect is well known. The effect of pilocarpine is an example. The

16 Suschtschinsky, P. Ueber den Einfluss des erhöhten und verminderten Blutdruckes und der veränderten Ernährung des Herzens auf die Erregbarkeit der peripherischen Endigungen des N. vagus in Herzen, *Centralbl f d med Wissensch* 6 33, 1868.

17 Starling, H. J. Heart Block Influenced by the Vagus, *Heart* 8:31, 1921.

18 Parry, C. H. An Inquiry into the Symptoms and Causes of the Syncope Anginosa, Commonly Called Angina Pectoris, London, Cadell & Davis, 1799, vol. 8.

19 Concoto, cited by Braun and Samet²³.

20 de Cereville, cited by Braun and Samet²³.

21 Wenckebach, K. F., and Winterberg, H. Die unregelmässige Herztätigkeit, Leipzig, Wilhelm Engelmann, 1927, p. 128.

22 Daniélopou, D., and Missirlin, V. Excitabilité centrifuge du vague dans les hypertones générales et les lésions chroniques du coeur. Valeur diagnostique et pronostique de l'épreuve du vague dans ces affections, *Compt rend Soc de biol* 92 538, 1925.

23 Braun, L., and Samet, B. "Vagusdruck" und Koronargefäss (Ein klinischer und experimenteller Beitrag zur Diagnose und Prognose der Herzkrankheiten), *Deutsches Arch f klin Med* 161 257, 1928.

presence of jaundice is another. Owen²⁴ showed that cardiac irregularities in dogs may be brought about by stimulation, or irritation of the hollow abdominal viscera when jaundice is present, whereas in non-jaundiced dogs no such irregularities occur on similar stimulation. It is conceivable that in various diseased states, as well as in persons with inherently vulnerable nervous systems, the resistance offered by the synapsis of the ganglion cells guarding the heart is lowered and vagal impulses are thus able to pass through freely, producing the phenomenon even in the absence of organic heart disease.

In view of the frequent occurrence of hyperactive cardioinhibition induced by carotid sinus stimulation in various conditions other than coronary disease, its application to the diagnosis of such disease is, of course, limited. Given, however, a person over 40 years of age who presents symptoms suggestive of the presence of coronary disease, a distinctly positive reflex may be considered an important corroborative finding. It appears as important as the electrocardiogram, which has its limitations and misleading implications.

As an abnormal manifestation, the hyperactive cardioinhibitory reflex, whether originating in the carotid sinus or elsewhere, deserves further investigation aside from its possible value as an aid in the diagnosis of coronary disease. The investigation should include especially the structural state of the ganglionic connections in the heart in those cases, a problem which has received no consideration in the past and the solution of which may explain the various cardiac arrhythmias and sudden, hitherto unexplained death.

SUMMARY

The normal carotid sinus mechanism is a protective adaptation to help maintain normal circulation. The adequate stimuli are changes in the intracarotid blood pressure. When the response to carotid sinus stimulation is unusually great, it is called a hyperactive carotid sinus reflex.

Hyperactivity may exhibit itself in extreme cardioinhibition, vaso-depression and cerebral manifestations.

This paper deals with an investigation of the hyperactive cardioinhibitory reflex in a series of 1,886 patients, including 1,151 males and 735 females. It was found that the reflex occurs with greater frequency and in higher degrees of response in males than in females. Its frequency and degrees of response also increase as age advances. Coronary disease is the most common condition in which the reflex occurs with the greatest frequency and the highest degrees of response. The more

24 Owen, S. E. A Study of Viscerocardiac Reflexes. The Experimental Production of Cardiac Irregularities by Visceral Stimulation, *Am Heart J* 8 496, 1933.

severe the coronary disease, the more apt the reflex is to occur and the greater its degree. Persons with other diseases and even some normal persons may present a hyperactive reflex, although not as often and to a much lesser degree.

It appears that the hyperactive cardioinhibitory carotid sinus reflex is due to lowered resistance at the synapses in the cardioinhibitory center and more so in the extracardiac and intracardiac ganglionic cells as well as in the myoneural junctions, allowing the transmission of afferent and efferent impulses in a large and at times an overwhelming volume. Coronary disease with its associated ischemia is a possible local cause for such lowering of resistance. An abnormal constitutional state and some defect in the nervous system may be other causes.

In view of the great frequency of a hyperactive reflex in coronary disease, it is recommended as a possible aid in the diagnosis of such disease in persons of the arteriosclerotic age who show suspicious signs or symptoms. It is also suggested that this reflex receive more study, since additional knowledge may help to explain the various cardiac arrhythmias and sudden, hitherto unexplained death.

TIME-ACTIVITY CURVES OF PROTAMINE ZINC INSULIN

CLINICAL APPLICATION AND SIGNIFICANCE OF SUCH CURVES
IN THE TREATMENT OF PATIENTS WITH
SEVERE DIABETES

HELEN EASTMAN MARTIN, M D

AND

PAUL O GREELEY, M D

LOS ANGELES

Among the roles played by insulin in carbohydrate metabolism, two have been stressed in previous publications from this laboratory¹. These roles may be summarized briefly as follows: (1) the control of new sugar formation in the fasting state, taken care of by the "basal insulin," and (2) the dextrose-disposing mechanism of insulin, operating by oxidation or storage.

It has been shown by many observers that the depancreatized dog in the fasting state has a high blood sugar level. The maintenance of a constant normal blood sugar level in the fasting diabetic dog requires the intravenous injection of insulin at the rate of 0.0051 to 0.035 unit per kilogram per hour, as shown by Greeley^{1a} and Houssay². Evidence that certain patients with severe diabetes may also have a rising blood sugar level in the fasting state has been reported by Martin, Drury and Strouse^{1c}. They showed that 0.5 to 3 units of regular insulin was required per hour to maintain the blood sugar within the normal limits. It was suggested by them that protamine zinc insulin is useful for this requirement.

The "dextrose-disposing" action constitutes a significant part of the activity of insulin; this function of insulin is primarily related to the

From the Departments of Physiology and Medicine of the School of Medicine of the University of Southern California and the Department of Medicine of the Los Angeles County Hospital (services of Dr. Solomon Strouse and Dr. Howard West).

1 (a) Greeley, P. O. The Basal Insulin Requirement in Depancreatized Dogs, *Am J Physiol* **120** 345-349 (Oct.) 1937. (b) Drury, D. R., and Greeley, P. O. The Measurement of Insulin Action, *ibid* **127** 581-588 (Oct.) 1939. (c) Martin, H., Drury, D. R., and Strouse, S. The Basal Insulin Requirement in Diabetes Mellitus, *Arch Int Med* **66** 78-92 (July) 1940.

2 Houssay, B. A., Lewis, J. T., and Foglia, V. G. Effet des injections continues d'insuline chez les chiens depancreates, *Compt rend Soc de biol* **101** 241-245 (May 24) 1929.

handling of dietary intake and, as suggested by Diury and Greeley,^{1b} should be studied on a time-activity basis. Insulin action is considered by them in the dynamic sense. "At any given time after an injection of insulin there is in the body a certain insulin activity which can be definitely measured by measuring the intravenous glucose rate just necessary to balance it at that time."

This paper is concerned with (1) time-activity curves of protamine zinc insulin in the depancreatized dog and in the patient with severe diabetes and (2) the clinical application of such curves to the basal insulin requirement and the dextrose-disposing insulin requirement for the diet of the patient with severe diabetes.

The procedure for determining the time-activity curve of insulin, as reported by Diury and Greeley,^{1b} in the depancreatized dog is, in brief, as follows. After a given dose of regular insulin, sufficient dextrose is administered intravenously or by mouth at hourly or half hourly intervals to keep the blood sugar level between 80 and 120 mg per one hundred cubic centimeters of blood. If the blood sugar level starts to fall, more dextrose is given, or, contrariwise, if too much dextrose has been given and the blood sugar level becomes elevated above normal no more dextrose is given until the blood sugar level has fallen to normal. Insulin activity is considered to be at an end if the blood sugar level rises when no dextrose is given, and more insulin is needed to cover the basal requirement. The method used for patients is essentially similar, but the dextrose is given by mouth in order to simulate more closely the conditions of dietary absorption.

In the following studies, determinations of blood sugar were made on venous blood by the Folin-Wu micromethod, unless otherwise stated. A brief summary of the animal's or patient's diabetic state and the conditions of the experiment are tabulated below each chart or table.

A time-activity curve of 50 units of protamine zinc insulin in the depancreatized dog is seen in figure 1. This chart shows: 1. The onset of activity of protamine zinc insulin was slow. No dextrose was required to cover insulin activity for the first three to four hours, during which time the blood sugar fell to a normal level, of about 100 mg per hundred cubic centimeters of blood. 2. The delayed peak of activity occurred between seventeen and twenty-four hours after the administration of insulin. 3. The duration of action was long, more than thirty-six hours. 4. A relatively small amount of carbohydrate was required per hour (average, 6 Gm per hour). 5. The total amount of carbohydrate required, 211 Gm of dextrose in thirty-six hours, was high, because of the long duration of action. 6. The fact that the blood sugar level is a reflection of the injection of dextrose, and insulin activity at any moment, is demonstrated at point *A*. Here, too much dextrose was given and the blood

sugar content was elevated. With decrease in the rate of administration of dextrose, the blood sugar dropped to the previous level. A need for basal insulin is indicated by the rising blood sugar level at point *B* after no dextrose had been administered for three hours. This point (*B*) also indicates the end of the activity of the 50 units of protamine zinc insulin.

This curve represents for the dog used the true time-activity curve of 50 units of protamine zinc insulin, since the animal was totally depancreatized and any unknown amount of insulin secreted from the pancreas could be eliminated from consideration.

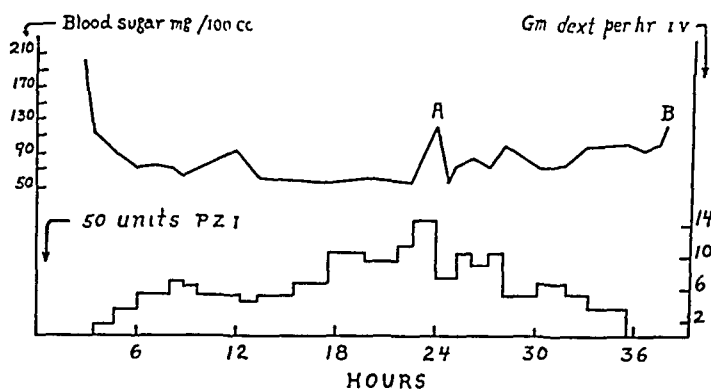


Fig 1—Measurement of the activity (the amount of dextrose that must be given per hour to keep the blood sugar level constant) of 50 units protamine zinc insulin in a diabetic dog

Protocol for figure 1

Diabetic dog Theo, female, wt 15 lbs (6.75 Kg)

Depancreatized 25 years previously

Regular regimen

9 a m 50 Gm sugar in soup
50 Gm meat
25 Gm pancreas
10 units regular insulin
5 p m Same as 9 a m
10 p m 50 Gm sugar in soup
10 units regular insulin

Preparation for experiment, diet and insulin day before the test

9 a m 50 Gm sugar in soup
50 Gm meat
50 Gm pancreas
10 units regular insulin
5 p m nothing to eat
4 units regular insulin
10 p m 4 units regular insulin

Condition of experiment Dog received no food during test except dextrose intravenously, as indicated on chart

Condition of dog Good

A time-activity curve of 100 units of protamine zinc insulin in a patient with severe diabetes is seen in figure 2. The general similarity of this curve (fig 2) to that found in the depancreatized dog (fig 1) is striking, indicating that in the main the shape of the curve may be interpreted as due to the activity of protamine zinc insulin rather than to the activity of insulin from the patient's pancreas. This chart demonstrates (1) the onset of measurable activity four hours after the injection of insulin was given, with the peak of activity occurring between

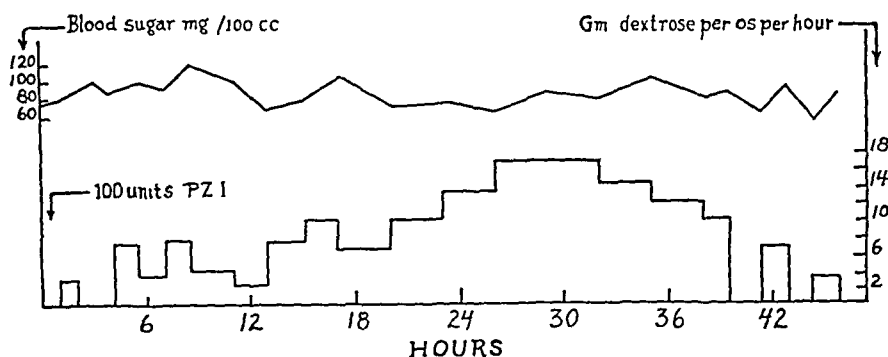


Fig 2—Measurement of the activity (the amount of dextrose that must be given per hour to keep the blood sugar level constant) of 100 units of protamine zinc insulin in a patient with severe diabetes

Protocol for figure 2

Patient J D, white, male, aged 55

Diabetes Known duration, three years

On regular insulin 20-0-20

Diet not known

Hospital entry Three weeks before study, in diabetic coma, precipitated by vomiting, diarrhea and discontinuance of insulin for three days

Hospital regimen before study

Diet	Carbohydrate	225 Gm
	Protein	80 Gm
	Fat	80 Gm

Insulin 50 units of protamine zinc insulin before breakfast for nine days before study

Glycosuria (day prior to study)

Slight trace of sugar 6 a m specimen single voided

Slight trace of sugar 9 a m specimen single voided

++ trace of sugar 3 p m specimen single voided

+++ trace of sugar 9 p m specimen single voided

Preparation for experiment Regular diet and insulin day before experiment

Condition of experiment Patient received no food during entire experiment

Condition of patient at time of experiment Good, patient ambulatory

twenty-four and thirty hours after injection, and with a duration of activity of more than forty-eight hours; (2) the minimum hourly dextrose requirement of 0 to 2 Gm, with a maximum of 16 Gm and an average of 8 Gm, and (3) the total dextrose requirement of 386 Gm in forty-eight hours

Figure 3 is the smooth curve obtained from figure 2 by roughly correcting the changes which occurred because of ingestion of too much or too little dextrose and represents the time-activity curve of 100 units of protamine zinc insulin in a given diabetic patient

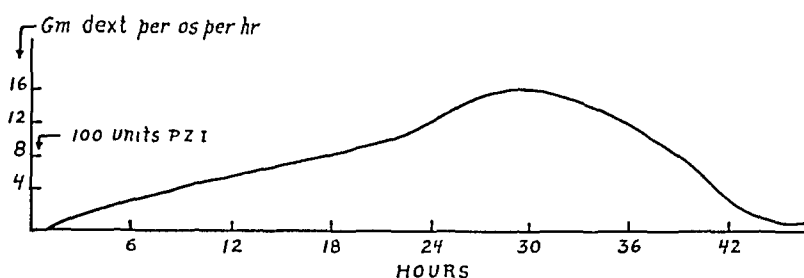


Fig 3—Time-activity curve of 100 units of protamine zinc insulin in a diabetic patient (approximated from results in chart 2)

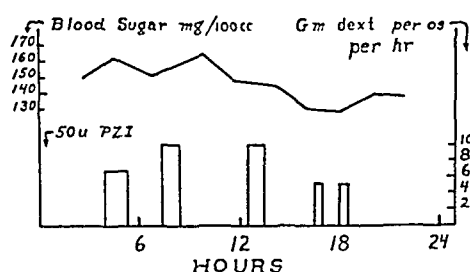


Fig 4—Measurement of activity of 50 units of protamine zinc insulin in a diabetic patient

Protocol for figure 4

Patient C K, white, male, aged 73

Diabetes Known duration, three years

On 30 units of protamine zinc insulin before breakfast

Diet Carbohydrate 125 Gm

Protein 60 Gm

Fat 80 Gm

Hospital entry Several weeks prior to study for foot infection

Hospital regimen before study

Diet Carbohydrate 125 Gm

Protein 60 Gm

Fat 80 Gm

Insulin 30 units protamine zinc insulin for eight days, 35 for two days, then 30 units protamine zinc insulin and 10 units regular insulin daily before breakfast

Glycosuria Variable, trace to 4 plus in all specimens

Preparation for experiment Regular diet and insulin day before experiment

Condition of experiment Patient received no food during entire experiment except dextrose administered orally, as indicated in chart

Condition of patient at time of experiment good, foot infection healed

Figure 4 is the time-activity curve of 50 units of protamine zinc insulin in another diabetic patient. This chart shows the small total amount of dextrose (35 Gm) required to maintain the blood sugar

between 137 mg and 167 mg per hundred cubic centimeters of blood during twenty-four hours

Figure 5 shows a somewhat similar time-activity curve, of 30 units of protamine zinc insulin in a third diabetic patient

The results of the attempt to obtain time-activity curves with smaller amounts of protamine zinc insulin in the depancreatized dog and a patient with severe diabetes are tabulated in tables 1, 2 and 3

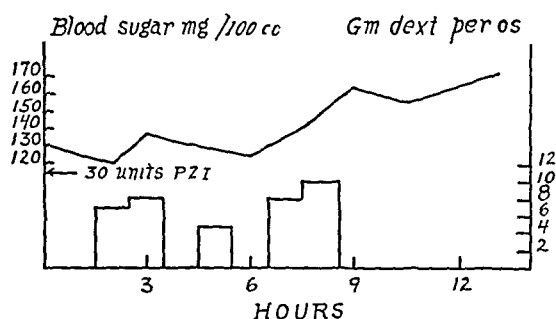


Fig 5—Measurement of the activity of 30 units of protamine zinc insulin in a diabetic patient

Protocol for figure 5

Patient L S, Mexican male, aged 53

Diabetes Known duration, two months On an unknown amount of insulin, two months Diet restricted, but amount unknown, two months

Hospital entry Twenty-four days before study, for gangrene in right foot

Hospital regimen

Amputation of right leg, three weeks before study

Diet	Carbohydrate	175 Gm
	Protein	70 Gm
	Fat	80 Gm

Insulin 15-15-15 regular insulin, following amputation, then changed to 40 units protamine zinc insulin for five days, then 30 units of protamine zinc insulin for two days before test

Glycosuria Occasional trace of sugar

Preparation for experiment Regular diet and insulin day before experiment

Condition of experiment Patient received no food during entire experiment except dextrose administered orally, as indicated in chart

Condition of patient at time of experiment Good

Table 1 shows the ability of 10 units of protamine zinc insulin to control the endogenous metabolism only in the fasting depancreatized dog. It is apparent that the blood sugar level never became low enough to require the administration of dextrose. The results are particularly interesting in view of the fact that this dog had been found on several previous examinations to have a high basal insulin requirement (about 0.5 units per hour or 12 units required in twenty-four hours). The 10 units of protamine zinc insulin controlled only this basal insulin requirement, as there was very little fluctuation of the blood sugar level during twenty-four hours, 190 to 266 mg per hundred cubic centimeters of blood. (It

is to be noted that this experiment was terminated before the insulin activity was completed, since the last determination of blood sugar showed a falling level)

TABLE 1—Control of the Basal Insulin Requirement in Spot, Depancreatized Dog, with Protamine Zinc Insulin (10 Units)

	Time	Blood Sugar, Mg in Each 100 Cc of Blood	Insulin, Units PZI *
6/1/39	8 18 a m	235	10
	8 20 a m		
	9 17 a m	194	
	10 00 a m	204	
	11 30 a m	190	
	1 04 p m	266	
	2 00 p m	235	
	3 06 p m	250	
	4 02 p m	266	
	8 40 p m	250	
	8 15 a m	210	
6/2/39 *			

* PZI, protamine zinc insulin

† Regular insulin

Protocol for table 1

Diabetic dog Spot, female, wt 14.5 Kg

Depancreatized 5 months previously Regular regimen

Diet $\frac{1}{3}$ of 400 Gm meat and 300 Gm sugar at 9 a m, 15 units RI †

$\frac{1}{3}$ of 400 Gm meat and 300 Gm sugar at 5 p m, 15 units RI †

$\frac{1}{3}$ of 400 Gm meat and 300 Gm sugar at 10 p m, 15 units RI †

Condition of experiment Dog received no food during entire experiment

Condition of dog at time of experiment Good

TABLE 2—Control of the Basal Insulin Requirement in Spot, Depancreatized Dog, with a Larger Dose of Protamine Zinc Insulin (Thirty Units)

	Time	Blood Sugar, Mg in Each 100 Cc of Blood	Insulin, Units PZI *
6/5/39	6 20 a m	263.1	30
	6 30 a m		
	8 30 a m	196	
	9 37 a m	200	
	10 58 a m	175.4	
	1 20 p m	143.9	
	2 47 p m	160	
	4 00 p m	166	
	5 45 p m	196	
	9 35 p m	222	
	10 00 a m	142	
	1 20 p m	227	
6/6/39	4 00 p m	230	

* PZI, protamine zinc insulin

† Regular insulin

Protocol for table 2 (see table 1)

Preparation for experiment Diet and insulin day before test

Diet 9 a m 200 Gm pancreas, 15 units RI †

200 Gm sugar

400 Gm meat

5 p m 75 Gm sugar in soup, 10 units RI †

10 p m 75 Gm sugar in soup, 10 units RI †

Condition of experiment Dog received no food during entire test

Condition of dog at time of experiment Good

Table 2 gives the results in the same dog after 30 units of protamine zinc insulin was given. While no dextrose was required to prevent hypoglycemia, even with the larger dose, there was considerably more fluctuation of the blood sugar level, 142 to 263 mg per hundred cubic centimeters of blood. (This experiment was also terminated before insulin activity was at end, since the blood sugar level during the last few hours of the experiment was stationary.)

TABLE 3—*Control of the Basal Insulin Requirement in Patient J S with Protamine Zinc Insulin*

	Time	Blood Sugar, Mg in Each 100 Cc of Blood	Insulin, Units PZI *
6/14/39	6 50 a m	172.4	40
	7 15 a m		
	10 40 a m	142.8	
	12 55 p m	163.9	
	3 50 p m	153.8	
	8 00 p m	142	
	11 00 p m	133	
6/15/39	1 16 a m	140	
	6 40 a m	206.2	

* PZI, protamine zinc insulin

† Regular insulin

Protocol for table 3

Patient J S, white, male, aged 16

Diabetes Known duration, four years

Insulin 20 units PZI* before breakfast, 20 units RI† before breakfast and dinner

Diet	Carbohydrate	200 Gm
	Protein	80 Gm
	Fat	100 Gm

Hospital entry Nine days before study, for infection of the respiratory tract
Hospital regimen

Diet	Carbohydrate	225 Gm
	Protein	90 Gm
	Fat	80 Gm

Insulin On regular insulin at first, then 40 units PZI* before breakfast for three days before test

Glycosuria Variable, but always moderate to large amounts of sugar present

Conditions of experiment

Patient on regular diet and insulin, day before test

7 p m, evening before test, 15 additional units RI† for glycosuria

12 p m, before test 20 additional units RI† for glycosuria

3 a m, four hours before test, orange juice, unknown amount for insulin reaction

Patient fasting throughout test

Condition of patient at time of experiment Good, although diabetes not well controlled

Similar results with small doses of protamine zinc insulin were obtained in several fasting patients with severe diabetes. Table 3 is illustrative of such studies and shows the fact that in a person with

severe diabetes 40 units of protamine zinc insulin was able to cover the basal insulin requirement only for eighteen hours. No dextrose was required to maintain a constant blood sugar level or to prevent hypoglycemia. The rising blood sugar content between the eighteenth and the twenty-fourth hour demonstrated the end of the activity of the 40 units of protamine zinc insulin and the fact that this patient had a basal insulin requirement. In another fasting, severely diabetic patient, who had been shown previously to have a basal insulin requirement of more than 2 units per hour, 40 units of protamine zinc insulin just met this requirement for eighteen hours. During this period the blood sugar content was between 100 and 160 mg per hundred cubic centimeters of blood (table not given).

The major clinical significance of these time-activity curves of protamine zinc insulin lies in the fact that they represent the amount of dextrose which will be required to maintain a normal blood sugar level during any time interval after an injection of insulin is administered. The practical import of this is the question whether a dietary schedule can be planned which will furnish dextrose at a rate which parallels the time-activity curves of large doses of protamine zinc insulin (50 to 100 units). It is known from numerous studies that ingested carbohydrate is quickly absorbed in from one-half to two or three hours while the absorption and conversion of proteins to amino acids (and thence, in part, to dextrose) occur between two and five hours³. Fat indirectly affects the dextrose absorption rate, since it slows the absorption of protein and carbohydrate. Any mixture of foodstuffs is known to delay the absorption of each constituent, and this is particularly true of fat³. The dextrose derived from the carbohydrate and protein of an ordinary mixed diet reaches the peak of absorption in two to three hours and then gradually falls to an end within five to eight hours. Campbell⁴ spoke of this as the "glucose load on the pancreas". A dextrose absorption rate which will parallel the activity of moderately small doses (under 50 units) of protamine zinc insulin in a person with mild or moderately severe diabetes may be obtained by the use of high protein-high fat diets⁵ or carbohydrate feedings at intervals⁶. With larger doses (over 50 units) of protamine zinc insulin, the time-activity curves illustrate graphically the reason for the conclusions which

3 Lusk, G. The Elements of the Science of Nutrition, ed. 4, Philadelphia, W. B. Saunders Company, 1928.

4 Campbell, W. R. Some Difficulties in the Use of the Insulins in Diabetic Practice, *Bull. New York Acad. Med.* **15** 579-596 (Sept.) 1939.

5 Pollack, H., and Dolger, H. Advantages of Proinsulin (Protamine Zinc Insulin) Therapy. Dietary Suggestions and Notes on the Management of Cases, *Ann. Int. Med.* **12** 2010-2021 (June) 1939.

6 Protamine Insulin and Diet in Diabetes Mellitus, editorial, *Ann. Int. Med.* **11** 2048-2050 (May) 1938.

many clinicians have reached empirically regarding the treatment of patients with severe diabetes.⁷ These conclusions are 1 Large doses frequently cause hypoglycemia in the postabsorptive period 2 More

TABLE 4—*Study of One Hundred Units of Protamine Zinc Insulin in Relation to Diet in Patient J D*

Time	Blood Sugar, Mg in Each 100 Cc of Blood	Diet	Urine	Insulin, Units PZI *
10/15/39		C 250 Gm P 85 Gm F 60-70 Gm		
7 50 a m	153 S			
7 55 a m				100 (in 2 injections of 50 units each)
8 35 a m		Breakfast, 1/5 carb		
9 55 a m	277 S			
8 30 a m to 11 30 a m			400 cc = 1.4 Gm	
11 40 a m	263.2			
12 00 a m		Lunch, 2/5 carb		
1 45 p m	310			
11 30 a m to 4 30 p m			500 cc = 4.8 Gm	
4 40 p m	250			
5 00 p m		Dinner, 2/5 carb		
6 40 p m	266.6			
9 10 p m	156			
10/16/39				
1 00 a m	123			
4 30 p m to 2 00 a m			800 cc = 0 Gm	
3 00 a m	105			
5 00 a m	133			
5 30 a m	148			
2 00 a m to 5 30 a m			250 cc = 0 Gm	

* PZI, protamine zinc insulin

Protocol for table 4 (see also protocol for figure 2)

Patient J D, white, male, aged 55

Diabetes Known duration, three years

Insulin 65 units PZI[†] before breakfast

Diet	Carbohydrate	250 Gm
	Protein	85 Gm
	Fat	60-70 Gm

Glycosuria Moderate

Hospital entry For study while on diet, no complaints

Preparation for experiment None

Condition of patient at time of experiment Good

7 Joslin, E P, Root, H F, White, P, and Marble, A The Treatment of Diabetes Mellitus, ed 6, Philadelphia, Lea & Febiger, 1937 Boyd, J D, and Jackson, R L Levels of Control in the Treatment of Diabetes Mellitus, I A M A 111 906-909 (Sept 3) 1938

quickly acting insulins are required to cover the dietary load if post-prandial hyperglycemia is to be avoided in the patient with severe diabetes. The curve of activity, in other words, does not parallel the

TABLE 5—*Study of One Hundred Units of Protamine Zinc Insulin in Relation to Diet in Patient C McF*

Time	Blood Sugar, Mg in Each 100 Cc of Blood	Diet	Urine	Insulin, Units PZI *
10/12/39		O 150 Gm P 65 Gm F 80 Gm		
6 30 a m				100
7 15 a m		Breakfast, 1/5 carb		
9 15 a m	183			
10 45 a m	123			
11 00 a m		Lunch, 2/5 carb		
8 30 a m to 1 00 p m			1,100 cc = 13.8 Gm	
1 10 p m	240.4			
3 50 p m	252			
1 00 p m to 3 50 p m			670 cc = 2.9 Gm	
4 30 p m		Dinner, 2/5 carb		
6 50 p m	294			
3 50 p m to 7 00 p m			1,600 cc = 11.75 Gm	
11 20 p m	181.8			
7 00 p m to 11 30 p m			750 cc = 8.3 Gm	
10/13/39				
3 40 a m	173.9			
5 45 a m	146			
11 30 p m to 5 30 a m			400 cc = 2.64 Gm	
5 30 a m to 8 15 a m			125 cc = 0.21 Gm	

* PZI, protamine zinc insulin

Protocol for table 5

Patient C McF, white, female, aged 24

Diabetes Known duration, seven years

Insulin 60 units PZI* before breakfast plus 20-0-10 (crystalline)

Diet Carbohydrate 100 Gm

Protein 60 Gm

Fat 80 Gm

Glycosuria Unknown amount, patient stated control fair

Hospital entry Four weeks before this study, for a vulvar abscess which healed several weeks before this study

Hospital regimen

Diet Carbohydrate 150 Gm

Protein 65 Gm

Fat 80 Gm

Insulin 80 units PZI* plus 15-10-5, four days before study

Glycosuria Variable, but large amounts in a m

Preparation for experiment None

Condition of patient at time of study Good, although in process of having teeth extracted, 2 extracted one week before study and 2 extracted one day before study

TABLE 6—Study of Eighty Units of Protamine Zinc Insulin in Relation to Diet in Patient H R

Time	Blood Sugar, Mg in Each 100 Cc of Blood	Diet	Urine †	Insulin, Units PZI ‡
6/26/39		C 191 Gm P 73 Gm F 81 Gm		
4 00 p m				80
6/27/39				
6 00 a m	33 *	25 Gm dex- trose § 1 v	70 cc = ++	Convulsions
7 30 a m		Breakfast, 1/5 carb		
9 00 a m	267			
9 30 a m			155 cc = ++	
11 15 a m	173	Lunch, 2/5 carb		
1 15 p m	250			
1 30 p m			90 cc = ++++	
4 00 p m				80
4 30 p m		Dinner, 2/5 carb		
6 30 p m	400			
7 00 p m			? no cc = ++++	
10 35 p m	210			
11 00 p m		Sandwich, C 15, P 8, F 7 §		
6/28/39				
1 00 a m	200			
3 30 a m	112			
4 00 a m	66	Orange juice, 4 oz §		
5 00 a m		Orange juice, 4 oz §		

* Benedict method of blood sugar determination

† All urine specimens recorded are single specimens

‡ PZI, protamine zinc insulin

§ In addition to diet

** RI, regular insulin

Protocol for table 6

Patient H R, white, male, aged 14

Diabetes Known duration, seven years

Diet	Carbohydrate	180 Gm
	Protein	80 Gm
	Fat	90 Gm

Insulin PZI † 40 units, RI ** 14 units

Glycosuria 2-3 per cent

Hospital entry Six weeks before study, for traumatic injury to wrist

Hospital regimen

Diet	Carbohydrate	180 Gm
	Protein	80 Gm
	Fat	90 Gm

Insulin 70-85 units PZI † late afternoon or evening, occasionally supplemented with 10-15 units RI **

Preparation for experiment None

Condition of patient at time of study Satisfactory, except for poor control of diabetes

abrupt rise in the absorption of dextrose after a meal or the sharp fall in the postabsorptive period

A few studies of persons with severe diabetes on a restricted diet and very large doses of protamine zinc insulin will serve to illustrate these points

Tables 4 and 5 show for 2 different diabetic patients the marked postprandial hyperglycemia occurring after each meal, even with the use of 100 units of protamine zinc insulin. The inability of 80 units of protamine zinc insulin to handle carbohydrate in the diet without the occurrence of marked hyperglycemia in another patient with severe diabetes is seen in table 6. Alternating with these periods of hyperglycemia are those of distinct hypoglycemia in the postabsorptive interval. To smooth out these large diurnal swings of blood sugar level (33 to 400 mg per hundred cubic centimeters of blood), this patient would require properly spaced frequent feedings

SUMMARY

The importance of measuring insulin action on a time-activity basis is discussed

Time-activity curves of large doses of protamine zinc insulin in the depancreatized dog and in the patient with severe diabetes are presented. These curves show graphically (1) the slow onset of activity, with delayed peak of activity, (2) the long duration of action, and (3) the relatively small amount of carbohydrate required per hour, as compared with the large total amount of carbohydrate required

The clinical application of such curves is discussed, with particular reference to (1) the excellent control of the basal insulin requirement of certain patients with severe diabetes by use of protamine zinc insulin in amounts under 40 units, and (2) the necessity of using more quickly acting insulins to cover the dietary load in patients with severe diabetes if postprandial hyperglycemia is to be avoided

Progress in Internal Medicine

ALLERGY

A REVIEW OF THE LITERATURE OF 1940

FRANCIS M RACKEMANN, MD

Lecturer in Medicine, Harvard Medical School

BOSTON

Allergy means literally a strange reaction exhibited by the body to a wide variety of foreign substances. The results of it touch almost every field of medicine, and it is not surprising that the literature increases tremendously. Any review of this literature either must attain the size of a large book like Sulzberger's new volume, entitled "Dermatologic Allergy,"¹ which, as its name indicates, covers only a portion of the entire subject, or else must consist of a summary of a few articles chosen according to the special interests of the compiler. Several summaries have appeared during the year. Simon² presents an excellent outline in Nelson's "Specialties in Medical Practice." Rowe³ has a new chapter on bronchial asthma in "Nelson New Loose Leaf Medicine." S. Feinberg and Bernstein⁴ have reviewed one hundred and twenty-two articles on asthma and hay fever contributed during 1939, and Harten and Walzer⁵ have summarized an even larger number of papers on serum allergy. If this present review dwells on certain aspects of allergy it is chiefly because I personally find them of greater interest, and my casual treatment of other aspects does not imply that another writer with other interests would not place his emphasis in other directions.

The symptoms of allergy are brought on by contact with some offending substance to which a patient is hypersensitive. How did he "get that way," and what is the nature of the process by which the symptoms develop? One talks about "the allergic state" and "the typical allergic person" and in doing so implies that there is in the patient a particular

From the Allergy Clinic and Laboratory, Massachusetts General Hospital

1 Sulzberger, M. B. *Dermatologic Allergy. An Introduction in the Form of a Series of Lectures*, Springfield, Ill., Charles C. Thomas, Publisher, 1940

2 Simon, F. A. *Allergy*, in Allen, E. van N. *Specialties in Medical Practice*, New York, Thomas Nelson & Sons, 1940

3 Rowe, A. H. *Bronchial Asthma*, in Nelson *New Loose Leaf Medicine*, New York, Thomas Nelson & Sons, 1939, vol. 3, chap. 6, p. 453

4 Feinberg, S. M., and Bernstein, T. B. *Asthma and Hay Fever. Contributions During 1939*, *J. Allergy* **11** 281, 1940

5 Harten, M., and Walzer, M. *Serum Allergy*, *J. Allergy* **11** 68, 1939

capacity for the development of sensitiveness to substances in his environment and that this capacity is the essential reason for all the manifestations of his disease. That a special capacity exists is attested by studies of the progress of the condition and the ultimate fate of the patient. The child with eczema is more likely to have hay fever or asthma develop in later life than is the normal child. That sensitiveness is directed to a variety of different substances to produce a number of different manifestations—eczema and asthma, for example—at the same time is strong evidence of a fundamental background. Here is the real problem in allergy. Hill⁶ reminds one of the vast difference between “being allergic,” by which he means the ability to show a positive reaction to a cutaneous test, and “being a sufferer from allergic diseases.” Something about the incidence of allergy, that is, of allergic symptoms, in the general population is known. It is recognized that the condition is often inherited, but otherwise little of the fundamental background is understood.

Brem and Colmes⁷ have studied the families of allergic children and find that the symptoms of allergy as well as the positive reactions to cutaneous tests are more frequent in these families than in a control group of normal families. On the other hand, there is increasing evidence to show that the symptoms of allergy, like those of hay fever and asthma, may develop even without a predisposition or any special tendency. For example, Hill⁸ finds that when the nursing infant is weaned to cow's milk, precipitins and positive reactions to cutaneous tests as well as eosinophilia will develop normally in from ten to twenty days after the start of the new feeding. These changes, however, are all temporary, and after several months the antibodies, the reactions to the cutaneous tests and the eosinophilia all clear away. During the period there may be trouble from asthma or eczema, but, in most cases, the objective changes occur without evidence of clinical disease. The reaction is allergic, just as serum disease is allergic, but it is a normal process occurring in a normal person.

Similarly, in the case of pneumonia, Wood⁹ has described in simple language and clear argument the development of antibodies and of positive reactions to cutaneous tests and their significance in showing the

6 Hill, L. W. Critical Review. Immunologically Altered Skin Reactivity in Nonatopic Persons, *J. Allergy* **11** 170, 1940.

7 Brem, J., and Colmes, A. Clinical and Potential Allergy in Families with Allergic Children, *New England J. Med.* **223** 329, 1940.

8 Hill, L. W. Milk as an Allergen, read at the Boston Allergy Round Table, June 14, 1939, footnote 6.

9 Wood, W. B. The Control of the Dosage of Antiserum in the Treatment of Pneumococcal Pneumonia. I. A Study of the Mechanism of the Skin Reaction to Type Specific Polysaccharide, *J. Clin. Investigation* **29** 95, 1940, II. The Clinical Application of the Francis Skin Test, *ibid.* **29** 105, 1940.

mechanism of this typical infectious disease, here again is a reaction occurring in a normal person. More on this subject will be presented later.

The actual development of clinical sensitiveness depends largely on the duration of exposure to the particular foreign substance. Clarke and Leopold¹⁰ show two curves which contrast the age at onset of hay fever among persons born in America with the age at onset among those born in foreign countries. The age among the latter was much greater. If, however, the length of residence of the foreigners in the United States is compared with the age of onset of those born in America, the curves for the two are almost identical. In each case the time factors were determined by the amount and duration of exposure.

In similar fashion, Phillips¹¹ notes the sharp increase in the number of persons near Phoenix, Arizona, who have become sensitive to the pollen of the newly encountered sugar beet. Up to 1936 there was little sugar beet in Arizona, but at that time 1,800 acres (7.3 square kilometers) were planted, and two years later Phillips identified 109 patients sensitive to the sugar beet pollen.

Buffum and B. Feinberg¹² followed the development of asthma in three pairs of identical twins. The age of onset, the severity of the asthma and the particular allergens concerned were similar in the members of each pair, but they were not identical and the variations depended on differences in exposure.

In the meantime, three papers point to new routes by which sensitiveness can be induced. Garver¹³ found that 3 nonallergic recipients were easily sensitized by giving them transfusions of 500 cc. of whole blood from an allergic donor. Reactions to cutaneous tests, which were negative before, became positive after the transfusion, were strongest on the fourth or fifth day and persisted for about two weeks. The symptomatic sensitivity was not tested. By the method of studying the reactions in passively sensitized sites on the skin, Gray and Walzer¹⁴ showed that peanuts ground in water and injected into the rectum were absorbed sufficiently by the normal person to induce a reaction in the previously sensitized site within sixteen minutes. In another experiment, Walzer¹⁵

10 Clarke, J. A., and Leopold, H. C. Effect of Pollen Contact upon the Age of Onset of Hay Fever, *J. Allergy* **11** 494, 1940.

11 Phillips, E. W. Time Required for the Production of Hay Fever by a Newly Encountered Pollen, Sugar Beet, *J. Allergy* **11** 28, 1939.

12 Buffum, W. P., and Feinberg, B. Bronchial Asthma in Three Pairs of Identical Twins. Special Reports, *J. Allergy* **11** 604, 1940.

13 Garver, W. P. The Transference of Reagents in Blood Transfusions, *J. Allergy* **11** 32, 1939.

14 Gray, I., and Walzer, M. Studies in Absorption of Undigested Protein in Human Beings, *J. Allergy* **11** 245, 1940.

15 Walzer, A. A Direct Technique for Demonstrating the Percutaneous Absorption of Antigens, *Arch. Dermat. & Syph.* **41** 692 (April) 1940.

showed that foreign protein suspended in a petrolatum base and rubbed into the skin of one arm would cause a wheal to develop at a passively sensitized site in the opposite arm. The antigen had been absorbed directly through the unbroken skin. Foreign protein can enter the body through various routes.

Meantime, the symptoms of asthma have been produced in guinea pigs by Ratner,¹⁶ who repeated previous experiments in which animals were exposed to a dust of dried horse dander or to a fine spray of dander extract. Exposure caused the development of sensitiveness, and after an interval a reexposure to the dust or spray caused symptoms of asthma in the animals so sensitized.

Do the manifestations of allergy appear only in certain persons? There are various experiments which throw light on the subject, but in interpreting their significance, one must be careful to distinguish between those factors which might alter the primary tendency for sensitiveness to develop in an animal and those other factors which are concerned with the elicitation of symptoms.

In previous reviews, I¹⁷ have pointed repeatedly to the difference between the rat and the guinea pig as illustrating the difference between those few persons in whom the signs of clinical allergy develop easily and the many others in whom there is no tendency for sensitiveness to develop. The rat can be sensitized with great difficulty, if at all, whereas the guinea pig is very susceptible to the effect of the injection of foreign protein. Various hypotheses have been offered to explain the difference in the reactions of the two animals and, more important, to explain the variation in the reactions of certain human beings.

VITAMINS

The vitamins form the basis of one hypothesis which holds that variations in feeding and nutrition can determine the development of allergy in a person. Vitamin C has been studied more than the other vitamins. Previously, Sulzberger and his associates¹⁸ have noted a

16 Ratner, B. Experimental Asthma, *Am J Dis Child* **58** 699 (Oct) 1939.

17 Rackemann, F. M. (a) Allergy. Review of Current Literature, *Arch Int Med* **55** 141 (Jan) 1935, (b) Review of Literature of 1935, *ibid* **57** 184 (Jan) 1936, (c) Review of Literature of 1936, *ibid* **59** 144 (Jan) 1937, (d) Review of Literature of 1937, *ibid* **61** 129 (Jan) 1938, (e) Review of Literature of 1938, *ibid* **63** 173 (Jan) 1939, (f) Review of Literature of 1939, *ibid* **65** 185 (Jan) 1940.

18 Sulzberger, M. B., and Oser, B. L. Influence of Ascorbic Acid of Diet on Sensitization of Guinea Pigs to Neoarsphenamine, *Proc Soc Exper Biol & Med* **32** 716, 1935. Sulzberger, M. B., and Mayer, R. L. Sensitizations, *Arch Dermat & Syph* **24** 537 (Oct) 1931.

marked variation in the ease with which certain groups of guinea pigs accept an active sensitization of the skin, and they have been able to show that this variation depended to a large extent on the way in which the animals were fed. Whether the differences concern the primary sensitization or the suppression of the subsequent reaction is hard to say, but in a recent discussion, Sulzberger has recalled the experiment of Cormia,¹⁹ who worked on experimental arsphenamine dermatitis in guinea pigs and found that the animals became sensitive without regard to the amount of vitamin C in their diet. The demonstration of the reaction, however, was closely concerned with vitamin C. High doses inhibited the reaction, but the animals were proved to be sensitive, since later the doses of ascorbic acid were reduced nearly to the scorbutic level and then the reactions became positive.

Bronfenbrenner²⁰ and his co-workers have studied the development of sensitiveness in guinea pigs which were fed large amounts of egg white by mouth and which at the same time were given a diet containing varying quantities of vitamin C. In a group of animals fed on a general diet with plenty of vitamin C no sensitization occurred, but in another group of animals fed on a scorbutogenic mixture sensitiveness could be elicited easily. That a part of the same group of animals could be protected by injections of large amounts of ascorbic acid is an important part of the experiment. The discussion of this paper was good. It was said that vitamin A may perhaps be quite as important as vitamin C. Moreover, S. Feinberg,²¹ who had also conducted feeding experiments on anaphylaxis in the rat, declared that animals on a diet deficient in vitamin E became susceptible to anaphylaxis, but when the vitamin was replaced their susceptibility disappeared. To him, Feinberg stated, wheat germ oil was important, and then he added, sorrowfully, that the feeding of wheat germ oil in large quantities to his patients had not seemed to help them. Further discussion recalled the early observations of Schloss and Worthen²² that sensitiveness develops in marasmic infants more often than in normal ones. Perhaps the withdrawal of vitamin C results merely in a change in the permeability of the intestinal mucosa. Shaw and Thelander²³ present further evidence that vitamin C is con-

19 Cormia, F. E. Experimental Arsphenamine Dermatitis. Influence of Vitamin C in Production of Arsphenamine Sensitiveness, *Canad. M. A. J.* **36** 392, 1937.

20 Bronfenbrenner, J., Hetler, D. M., Love, F. M., and Burnett, J. M. Experimental Alimentary Allergy and Its Prevention, *J. Allergy* **11** 466, 1940.

21 Feinberg, S. M., in discussion on Bronfenbrenner and others²⁰.

22 Schloss, O., and Worthen, T. W. The Permeability of the Gastro-Enteric Tract of Infants to Undigested Protein, *Am. J. Dis. Child* **11** 342 (May) 1916.

23 Shaw, E. B., and Thelander, H. E. Importance of Sensitization Mechanism in Clinical Phenomenon of Allergy. Possible Cause and Prevention, *Am. J. Dis. Child* **58** 581 (Sept.) 1939.

cerned with the development of clinical allergy in man. Would it not be interesting to find that hay fever, asthma and eczema depended on nothing more important than the inadequate feeding of certain vitamins in the early years of life?

HISTAMINE

Another theory to explain the symptoms of allergy is the concept that allergic persons are more susceptible to the action of histamine than are normal persons. Histamine makes the uterus of the normal guinea pig contract. On intravenous injection it causes a marked fall in the blood pressure of the cat and a severe bronchospasm in the guinea pig. Applied to a scratch in the skin of man and animals, it causes an immediate wheal and an erythema reaction. All of these effects are quite like those produced by the specific allergen applied to sensitive persons, and so comes the theory often discussed that the symptoms of allergy excited by a wide variety of different causes depend ultimately on the release of histamine from the sensitized cell as a result of the injury incidental to the union of antigen and antibody on the surface of that cell. There is no doubt but what histamine *can* produce all of these effects, but whether it *does* produce them during normal natural processes is another matter. The blood and lymph taken from dogs during anaphylactic shock, the perfusion fluid containing antigen which has been passed through the isolated lungs in sensitized guinea pigs, as well as the extracts of various tissues from animals in shock—all of these materials reveal physiologic activities when tested on the isolated intestine of the guinea pig or on the blood pressure of the cat which suggest that they contain histamine.

It is fair to note, however, that another substance, acetylcholine, is also present in normal tissue and has a physiologic effect which is similar to that of histamine. I submit that one must be critical of results which lead to the claim that histamine is the responsible factor when these are based simply on physiologic experiments. One must be quite certain that the blood or the tissue extract to be tested has been boiled so as to destroy the acetylcholine, which is so unstable. Histamine will withstand boiling even in the presence of acid. However, chemical identification of histamine has been accomplished in a few instances. The first successful attempt was made by Barger and Dale²⁴ in 1910. In 1919 Abel and Kubota²⁵ isolated histamine dipicrate from dried

24 Barger, G., and Dale, H. H. Chemical Structure and Sympathomimetic Action of Amines, *J. Physiol.* **41** 19, 1910.

25 Abel, J. J., and Kubota, C. On the Presence of Histamine b-Iminazolyethylamine in the Hypophysis Cerebri and Other Tissues of the Body and Its Occurrence Among the Hydrolytic Decomposition Products of Proteins, *J. Pharmacol. & Exper. Therap.* **13** 243, 1919.

pituitary material, but it was not until 1927 that Best, Dale, Dudley and Thorpe²⁶ prepared histamine in crystalline form from normal tissues. In tissues, acetylcholine is quickly destroyed by a normal ferment called cholinesterase. This destruction, however, can be blocked by the addition of small quantities of physostigmine, also called eserine. Furthermore, the effect of atropine is critical. On the reaction to histamine atropine has no effect, but if administered after acetylcholine, atropine blocks its physiologic action at once. The absence of benefit from atropine in patients with asthma argues for the histamine theory. Finally, one can say that histamine is released from the cell as the result of mechanical injury, whereas acetylcholine is released only as a result of nerve stimulation. This is the reason why acetylcholine is more easily obtained from organs rich in nerve tissue. One theory is that both effectors play their parts—nerve stimulation releases acetylcholine, which in turn stimulates the local cells to release histamine. Alexander²⁷ discusses this in an interesting paper.

Clinical studies on histamine are limited for the most part to determinations of the amount in the circulating blood. The method of determination is difficult because the tiny quantities can be estimated only by physiologic experiments on an isolated segment of guinea pig intestine. The response of the muscle to the unknown solution is compared with the response to a standardized solution with a known histamine content, and the quantities of the unknown are adjusted until the two become equal.

In animals in anaphylactic shock, several studies of the histamine levels in the blood have been made. In guinea pigs and dogs, Code²⁸ showed that there was a marked increase in the histamine content of the blood during shock but that it was transient, lasting only for a few (ten to twenty) minutes. The fall in blood pressure is coincident with the rise in histamine. In the horse, however, Code and Hester²⁹ found that the histamine content of the blood fell to zero, and, similarly, in the calf histamine virtually disappeared from the blood during anaphylactic shock. Incidentally, the sheep and the goat suffered no shock at all, the content of histamine in their blood was unchanged after the second dose of foreign protein, whether egg white or horse serum was

26 Best, C. H., Dale, H. H., Dudley, H. W., and Thorpe, W. V. Nature of Vaso-Dilator Constituents of Certain Tissue Extracts, *J. Physiol.* **62**:397, 1927.

27 Alexander, H. L. Allergic Syndromes in the Absence of Allergens, *J. Allergy* **11**:163, 1940.

28 Code, C. F. The Histamine Content of the Blood of Guinea Pigs and Dogs During Anaphylactic Shock, *Am. J. Physiol.* **127**:78, 1939.

29 Code, F., and Hester, H. R. The Blood Histamine During Anaphylactic Shock in the Horse and Calf, *Am. J. Physiol.* **127**:71, 1939.

used In rabbits, Rose and Weil³⁰ found a marked decrease, but the correlation between the degree of shock and the amount of decrease in histamine in the blood was not close

Katz³¹ studied the release of histamine from the blood cells in anaphylaxis In a test tube he added the antigen (egg white) to quantities of blood from rabbits sensitized to egg and incubated the mixtures for ten minutes The histamine content was found to be increased from one to six times over the figure obtained from similar mixtures of egg white with blood from normal rabbits The findings suggest that the histamine had been released from the white cells into the plasma

Dragstedt and his associates³² point out that histamine can be released from cells in other tissues besides the blood—the lungs, for example, though the amount is relatively small In the meantime, Zon, Ceder and Crigler³³ find histamine present in quantities in the blood platelets of the rabbit More important is the paper by Martin and Valenta,³⁴ in which it is reported that the organs of the white rat contain histamine in quantities which are not very different from those found in comparable tissues of other animals As the authors say, this finding suggests that the resistance of the white rat to anaphylactic shock is, therefore, not due to a low histamine content

In man, determinations of the blood histamine have been continued In Montreal, Rose³⁵ has perfected his technic so well that he is able to make many determinations in a single day Rose has now studied 200 patients, 80 with typical allergy Normally the blood contains from 0.25 to 0.75 microgram of histamine per cubic centimeter Patients with urticaria and eczema and with true sensitiveness to cold have low blood histamine values The values for patients with asthma tend to run higher, and in one boy ill with this condition the value of 1.8 micrograms was obtained As he improved this value fell The changes, however, were not striking

In the review of last year, I^{17f} mentioned several reports of experiments on treating patients with allergy with injections of histamine, pre-

30 Rose, B, and Weil, P The Blood Histamine in the Rabbit During Anaphylactic Shock, *Proc Soc Exper Biol & Med* **42** 494, 1939

31 Katz, G Histamine Released from Blood Cells in Anaphylaxis in Vitro, *Science* **91** 220, 1940

32 Dragstedt, C A, de Arellano, R, and Lawton, A H The Relationship of Histamine to Anaphylaxis in the Rabbit, *Science* **91** 617, 1940

33 Zon, L, Ceder, E T, and Crigler, C W The Presence of Histamine in the Platelets of the Rabbit, *Pub Health Rep* **54** 1978, 1939

34 Martin, J, and Valenta, A The Histamine Content of the Organs of the White Rat, *Arch f exper Path u Pharmacol* **193** 305, 1939

35 Rose, B Blood Histamine Studies in Allergic Patients, read at the Annual Meeting of the Society for the Study of Asthma and Allied Conditions, Atlantic City, N J, May 4, 1940

sumably in order to increase their tolerance to it. This year, Farmer³⁶ has compiled an interesting review of the literature and describes 2 cases in which the results of treatment were good. Histamine phosphate was used, and the quantities were minute. Treatment began with 0.1 microgram, which may be expressed as 0.1 cc. of a 1 to 100,000 dilution, and the later doses amounted only to 200 micrograms, corresponding to 0.2 cc. of a 1 to 1,000 dilution.

Meantime, a derivative of acetylcholine, acetylbetamethylcholine chloride, also called mecholyl, has been used by Pearson³⁷ in the treatment of 7 patients sensitive to wheat, apparently with excellent results, for all were "desensitized." It is interesting that slight overdosage reproduced the symptoms, whether asthma, hay fever or eczema, of which the patient first complained.

"Histaminase" has attracted much attention. In 1930, Best and McHenry³⁸ found that when fresh extracts of various animals' tissues were added to solutions of histamine in the test tube, the physiologic effect of the histamine was greatly reduced. Since the neutralizing activity of the extract was destroyed by heating, they expressed the belief that the effect depended on an enzyme, and they named it histaminase. Later, the same fresh tissue was treated with acetone and ether and then dried rapidly before a fan to produce a stable powder. It was found that 200 mg. of this powder could inactivate 2 mg. of histamine when incubated with it for twenty-four hours. More recently, similar preparations made commercially have been used on a wide scale and solutions of the material have been dispensed in ampules. Karady and Browne³⁹ hold that if the contents of these ampules are injected into an animal just before a fatal dose of histamine, it will survive and, furthermore, that other animals sensitized to protein can be protected against a subsequent shock by the previous injection of histaminase. That these results did not depend on some nonspecific effect was shown by the fact that when the histaminase was inactivated at 56 C. for one hour all its protective power was lost.

The time element is always important. In the test tube destruction of histamine by the ferment requires between twenty-four and seventy-two hours, but in the living animal protection can be demonstrated within a few minutes after the injection of the histamine solution. Whether

36 Farmer, L. Histamine in Anaphylaxis and Allergy, *Bull. New York Acad. Med.* **16** 618, 1940.

37 Pearson, E. F. Clinical Desensitization to Wheat by Use of an Acetylcholine Derivative, *Ann. Int. Med.* **13** 2241, 1940.

38 Best, C. H., and McHenry, E. A. Inactivation of Histamine, *J. Physiol.* **70** 349, 1930.

39 Karady, S., and Browne, J. S. L. Effect of Histaminase Treatment on Histamine and Anaphylactic Shock in Guinea Pigs, *J. Immunol.* **37** 463, 1939.

this "protection" is really effective and whether it is specific are questions still under discussion

In the rat, Rose, Karady and Browne⁴⁰ have shown that when histamine is injected intravenously, it accumulates in the liver and especially in the kidney and from these organs it disappears gradually. This year they incubated mixtures of various rat tissues and histamine under toluene and then determined the ability of the tissue extracts to destroy the histamine. Histaminase was found present only in the lung and intestine of the rat, no destruction of histamine was produced by extracts of liver, kidney, spleen, stomach or blood. Evidently, then, the slow disappearance of injected histamine from the kidney of the rat depends on some mechanism other than the action of histaminase.

In the clinic, many experimenters have aimed to test the beneficial effects of histaminase. In the treatment of patients with physical allergy, including the so-called "cold allergy," Roth and Horton⁴¹ found that the drug is useful and effective. They sought to demonstrate its effect by an ingenious experiment. They determined the normal response of the gastric acids to an injection of histamine, then they found that if histaminase is applied to the duodenum through a tube thirty minutes before the dose of histamine, the normal rise of acidity is abolished. In patients with "cold allergy," placing the hands in cold water likewise causes an increase of gastric acids, which can be abolished by previous treatment with histaminase. Previously the authors⁴² had reported the case of a patient in whom the total gastric acids and the amount of free hydrochloric acid were reduced markedly by treatment with a commercial preparation of histaminase. On the other hand, in an earlier paper, Atkinson and Ivy⁴³ had failed to show that any inhibition of the gastric secretion occurred when histaminase was made according to the method of Best was given in doses which in the test tube were more than enough to inactivate

Baker,⁴⁴ however, described 2 patients whose cold allergy was successfully treated with histaminase. Forman⁴⁵ has given histaminase by

40 Rose, B., Karady, S., and Browne, J. S. L. The Histaminase Content of the Tissue of the Rat and the Effect of Histamine Pre-Treatment, *Am J Physiol* **129**:219, 1940

41 Roth, G. M., and Horton, B. T. Physiologic Effects of Histaminase and Histamine, *J A M A* **114** 522 (Feb 10) 1940

42 Roth, G. M., and Horton, B. T. Hypersensitiveness to Cold Treatment with Histamine and Histaminase, Report of Case, *Proc Staff Meet, Mayo Clin* **12**:129, 1937

43 Atkinson, A. J., and Ivy, A. C. Action of Histaminase on Gastric Secretory Response to Histamine and to a Meal, *Am J Physiol* **107**:168, 1934

44 Baker, T. W. Histaminase in Cold Allergy, *J A M A* **114** 1059 (March 23) 1940

45 Forman, J. The Use of Histaminase in the Treatment of Various Allergic Manifestations, *Ohio State M J* **36** 56, 1940

mouth to numbers of patients with urticaria, atopic dermatitis, asthma, and the like, and he reports good results in those patients who had a definite allergic background, but less good results in other, nonallergic patients. Miller and Piness⁴⁶ treated 42 patients, including 29 with urticaria, but no relief occurred except in 7, and in no instance could this relief be attributed unequivocally to the use of the enzyme.

Goldberg⁴⁷ treated 35 patients having allergic diseases of the skin with histaminase, giving the drug by mouth in 25 instances and by injection in 10. All of the patients were improved and some quite relieved, particularly by the injection method. It should be noted, however, that in many instances the first injection caused an increase in temperature, up to 102 F, and it is not unlikely that the good results may have depended on an effect which was quite nonspecific. Prickman and his associates⁴⁸ gave histaminase in tablet form ten minutes before meals to 29 patients suffering from chronic vasomotor rhinitis. Of these patients, 41 per cent had complete relief and 13 per cent were improved, but 45 per cent were unaffected. Keeney⁴⁹ found good results in certain persons with hay fever, but in each instance the clinical improvement occurred on a day when there was a distinct drop in the total pollen count, so that if improvement came it was hard to explain the reason for it.

Meantime, histaminase has been reported to cause untoward reactions. Scheef⁵⁰ had a patient with duodenal ulcer who was given commercially prepared histaminase parenterally, and in twenty minutes urticaria, asthma and conjunctivitis developed. Greenbaum⁵¹ observed 2 patients, both women in their thirties, who were likewise treated with histaminase by intramuscular injections. In 1 patient, when the second dose was given in the arm, twenty-eight days after the first, there was a tremendous swelling, which extended from the shoulder to the elbow and lasted for four days. The other patient was given three doses at four to five day intervals, after the third, not only did an extensive local reaction develop but the patient suffered from abdominal cramps, nausea, vomiting and diarrhea.

46 Miller, H, and Piness, G. Histaminase in the Treatment of Allergy, *J A M A* **114** 1742 (May 4) 1940

47 Goldberg, L. C. Histaminase in the Treatment of Allergic Dermatoses, *J A M A* **115** 429 (Aug 10) 1940

48 Prickman, L. E., Lillie, H. I., Roth, G. M., and Fleming, R. G. Results of the Use of the Intestinal Mucosa in the Treatment of Vasomotor Rhinitis, *Ann Int Med* **13**:2235, 1940

49 Keeney, E. L. Histaminase in the Treatment of Hay Fever, *J A M A* **114** 2448 (June 22) 1940

50 Scheef, A. Allergic Manifestations Following the Injection of Torantil, *Munchen med Wchnschr* **83**:1740, 1936

51 Greenbaum, S. S. Local Anaphylactic (Arthus?) Phenomena from Parenteral Injections of Histaminase, *J A M A* **115**:847 (Sept 7) 1940

The results of treatment with histaminase are in general disappointing, as shown by several other papers. Corper and Cohn⁵² showed that the previous injection of histaminase had no effect on the lethal shock to a subsequent dose of tuberculin given to sensitized animals. Incidentally, they found that neither by intravenous nor by intraperitoneal injection was it possible to protect animals against the fatal dose of histamine, whether given intravenously or intraperitoneally. Simon⁵³ calls attention to some of the discrepancies in the histamine-histaminase theory. He points out that Abramson and his associates⁵⁴ by means of an electric current could drive histamine through the unbroken skin to produce an allergic wheal and then by reversing the current could draw this histamine out again, but that when the wheal was produced by ragweed in a sensitive person, no histamine could be "recovered" when the current was reversed.

Simon recalls that Kline, Cohen and Rudolph,⁵⁵ in 1932, showed that the wheals produced by histamine were different histologically from typical allergic wheals. In his own experiment, Simon⁵³ mixed histamine and histaminase in a test tube and found that the reactions to cutaneous tests with the mixture were negative—the histamine had been destroyed. When, however, the histaminase was injected into the tissue, either before or after the dose of histamine, the reaction to the cutaneous test was positive, as usual. In the tissue there was no such neutralization as in the test tube. Moreover, his experiment in feeding histaminase to his patients with hay fever gave negative results.

Pertinent and important is a note to the Editor of *The Journal of the American Medical Association* from Drs. Best and McHenry,⁵⁶ in Toronto. In their laboratory, the administration of histamine to animals for a period of several weeks did not produce the increase in histaminase which would be expected if the treatment had caused an increased need for the enzyme. They also tried to protect guinea pigs against anaphylactic and histamine shock by the use of histaminase, but the results were negative throughout. Referring to the use of histaminase by mouth, they point out that the enzyme is inactivated by pepsin in acid

52 Corper, H. J., and Cohn, M. L. Effect of Histaminase on Histamine Intoxication, Tuberculo-Anaphylaxis and Tuberculo-Allergy, *J. A. M. A.* **115** 30 (July 6) 1940.

53 Simon, F. A. Experiments with Histaminase, *J. Invest. Dermat.* **3** 29, 1940.

54 Abramson, H. A., Engel, M., Lubkin, V., and Ochs, I. Reversed Iontophoresis of Histamine from Human Skin, *Proc. Soc. Exper. Biol. & Med.* **38** 65, 1938.

55 Kline, B. S., Cohen, M. B., and Rudolph, J. A. Histologic Changes in Allergic and Nonallergic Wheals, *J. Allergy* **3** 531, 1932.

56 Best, C. H., and McHenry, E. W. A Note on Histaminase, *J. A. M. A.* **115** 235 (July 20) 1940.

solution and by trypsin in slightly alkaline solution, so that it would be difficult to suppose that histaminase given orally could survive digestion. Finally, they say that over a period of ten years, their investigations have failed to show that the intravenous or the intramuscular injection of histaminase has any effect on the histamine in the body or on that given by injection, even though their preparations of the enzyme are at least four times as potent as any available commercially. The work on histaminase suggests a mechanism for the destruction of histamine in the body, but, after all, this is only one of several possible mechanisms. They believe that "there is no physiologic basis on which to rest the clinical use of histaminase."

SALTS AND WATER

Aside from the one theory that the allergic state depends on faulty nutrition, particularly on the lack of vitamins, and the other theory that it depends on an excess of histamine or perhaps on an inability to eliminate histamine, there is the third theory that simple salts play a part. Perhaps the amount of total salt in the body varies from the normal and so leads to a disturbance either in the acid-base balance or in the water content or in both at once, or perhaps changes in the relative amounts of one particular base allow the physiologic action of that base to become important. And so comes the suggestion that potassium might be useful in treatment.

In serum disease, as in acute infections, there is a slight but definite retention of salt and of water during the acute attack. In asthma, however, the opposite is true. There is a loss of water and sodium during the paroxysm. Sheldon, Howes and Stuart⁵⁷ have found that the loss of sodium might be as much as 3 to 5 Gm. more than the intake of sodium during the asthmatic period. During recovery, however, the sodium in the urine was much less than the sodium ingested, and so equilibrium was again established. The water metabolism followed the sodium changes, as might be expected, in spite of the fact that the pathologic basis of allergic manifestations includes a local increase in tissue fluid.

Stoesser and Cook⁵⁸ suggest a new treatment of asthma based on artificial changes in water balance. These authors had observed that a certain patient with intractable asthma was made worse by a high salt (sodium chloride) intake. They made a careful chemical study of 6

57 Sheldon, J. M., Howes, H., and Stuart, G. Observation on Total Water and Sodium Exchange in Asthmatic Patients, *J. Allergy* **11** 1, 1939.

58 Stoesser, A. V., and Cook, M. M. Electrolyte and Water Exchanges in Bronchial Asthma, with Emphasis on the Influence of Pitressin, *J. Allergy* **11** 557, 1940.

asthmatic children First they found that fever therapy in a "hot box" had good results when the intake of sodium chloride was reduced—and the body water depleted—but in other instances, when the intake of sodium chloride was normal, the fever did not have a beneficial effect Further study of the electrolyte and water balance was made with the help of pitressin, a pituitary substance with an antidiuretic action which can cause the retention of total body water The procedure in 1 of the cases was as follows A child with a chronic persistent type of asthma was given a diet low in potassium, sodium and chlorine (0.33, 0.12 and 0.18 Gm, respectively) and total fluids of 1,400 cc per twenty-four hours For a week there was no change in the asthma, and then on the eighth day pitressin was given and the fluid intake was increased to 2,600 cc by giving more water In twenty-four hours the asthma disappeared, and in thirty-six hours the patient had gained 1.5 Kg Then the pitressin was stopped and 2,000 cc of urine was excreted, but even so, the asthma did not return More and more food was given, until after a few months the salt intake again became too high, and asthma reappeared For other children, two or more courses of pitressin were necessary, and although extra water was not always given with the drug, the results were good

The authors' comment indicates the opinion that the changes in the asthma depend on the changes in the water balance and not in the salt metabolism Last winter, Kern⁵⁹ gave a lucid discussion of water balance before the Associated Allergy Clinics of Greater New York Total body water is influenced by many factors Acidosis causes loss in water, so does hyperglycemia, as well as chilling of the body and a rising barometric pressure Menstruation is sometimes associated with retention of water, due to the activity of the antidiuretic principle of the pituitary gland The symptoms of allergy depend on edema in the shock organ, and the effect is local In terms of local change the edema is extensive, but in terms of the body as a whole it is limited In the presence of a full water complement in the whole body, the allergic reaction can produce the symptoms a little easier, but not much, and, vice versa, if the water content is low, local allergic reactions may or may not be effective enough to cause trouble To produce acidosis or to feed a salt-poor diet is to encourage dehydration and so to discourage the effect of allergy, but it is not surprising that the effort is not oftener more effective

There are several difficulties with the idea that water balance plays any real part in the underlying cause of asthma First, as Kern remarks,

59 Kern, R. A. Role of Water Balance in Clinical Manifestations of Allergy, *Am J M Sc* 199:778, 1940

there is no evidence that attacks of asthma are preceded by any water retention. Second, I have observed a number of patients who came to the hospital with violent asthma, which had been in progress for some time, and who were obviously dehydrated. The skin and tongue were dry; the flesh was soft, and when a liter or two of physiologic solution of sodium chloride, usually with 5 per cent dextrose, was injected intravenously relief was definite and prompt. Also I have observed that when a cor pulmonale with passive congestion developed in some of these patients the asthma ceased as soon as edema appeared. My findings, therefore, are comparable with those of Stoesser and Cook. However, I agree with Kern that in asthma the changes in water balance described by Sheldon and his co-workers are more likely an effect of the process than a cause of it. They are not concerned with the fundamental cause of the disease.

Potassium has properties which justify its consideration as a factor in allergy. Potassium is more a constituent of cells, sodium, of extracellular fluids. Last year, Rusk and his associates⁶⁰ suggested that in allergy the potassium moves out of the cells (the serum potassium increases) and that treatment with insulin, with dextrose or with potassium chloride tends to restore the *status quo ante*. Talbott and Schwab⁶¹ have written an excellent review of the knowledge of potassium. This base has three principal roles. It is concerned with the acid-base balance between cells or blood, it is antagonistic to insulin and acts like epinephrine, and finally it is antagonistic to cholinesterase and, as the principal base in muscle cells, is concerned with the transmission of the nerve impulse. In allergy, any good effect of potassium might depend on its epinephrine-like action, for Camp and Higgins⁶² have shown that constriction of the bronchioles induced by histamine could be relieved as promptly by potassium salts as by epinephrine hydrochloride. Talbott and Schwab are inclined to the idea that by inhibiting the enzyme cholinesterase potassium allows the acetylcholine released by nerve impulses to exert its normal effect and so to improve vasomotor tone. Incidentally, Brewer, Larson and Schroeder⁶³ found that the injection of epinephrine hydrochloride produces a rapid though transient (one and a half minutes) rise in the content of potassium in the blood—a finding complementary to that of Camp and Higgins.

60 Rusk, H. A., Weichselbaum, T. E., and Somogyi, M. Changes in Serum Potassium in Certain Allergic States, *J. A. M. A.* **112**:2395 (June 10) 1939.

61 Talbott, J. H., and Schwab, R. S. Recent Advances in the Biochemistry and Therapeutics of Potassium Salts, *New England J. Med.* **222**: 585, 1940.

62 Camp, W. J. R., and Higgins, J. A. The Role of Potassium in Epinephrine Action, *J. Pharmacol. & Exper. Therap.* **57**: 376, 1936.

63 Brewer, G., Larson, P. S., and Schroeder, A. R. On the Effect of Epinephrine on Blood Potassium, *Am. J. Physiol.* **126**: 708, 1939.

Clinical reports on the results of treatment with potassium in allergic disease are numerous. They have all been prompted by Bloom's⁶⁴ original announcement that doses so small as 5 grains (0.32 Gm) of potassium chloride given three times a day were beneficial in treating hay fever. Not one of these reports is favorable. Rusk, Dean and Rindskopf⁶⁵ treated 30 patients with hay fever, and only 3 were relieved. However, several patients with other types of nasal allergy were benefited. The content of potassium in the blood was normal in all. Harsh and Donovan⁶⁶ treated 40 patients with hay fever and obtained good results in only 1 of the 40. In those instances in which the content of sodium and potassium in the serum was determined before and after treatment, there were no significant differences. Harley⁶⁷ gave potassium to 43 patients with various allergic complaints but obtained no favorable results. Rubin and others⁶⁸ in Feinberg's clinic treated 153 patients but found potassium of no value. Their article includes an excellent review of the literature. Miller and Piness⁶⁹ gave potassium in various doses to 40 patients with hay fever during the season of their symptoms. Two patients obtained some relief from the potassium mixture but even more relief from the soda solution used as a control. Spain, Westcott and Gaillard⁷⁰ tried hard to find some good effect of potassium chloride in hay fever, but with no success.

From this review, it is all too evident that the fundamental cause or background of allergy is still unknown. None of the theories advanced so far can be substantiated. And yet, the clinical picture of recurrent susceptibility, of the tendency for sensitiveness to develop, which characterizes patients must have a cause. Most, if not all, of the studies on patients deal with the results—the effects of the primary process. Perhaps, however, the day will come when these clinical observations will suggest another theory that will stand up under test, and so these observations must be pursued.

64 Bloom, B. The Use of Potassium Salts in Hay Fever. Preliminary Report, *J A M A* **111** 2281 (Dec 17) 1938.

65 Rusk, H. A., Dean, I. W., and Rindskopf, W. Results of Potassium Therapy in Nasal Allergy, *Ann Otol, Rhin & Laryng* **49** 17, 1940.

66 Harsh, G. F., and Donovan, P. B. Potassium Chloride in Allergic Disorders, *J A M A* **114** 1859 (May 11) 1940.

67 Harley, D. Note on Oral Potassium Chloride Therapy in Asthma, Hay Fever, Urticaria and Eczema, *J Allergy* **11** 38, 1939.

68 Rubin, S. S., Aaronson, A. L., Kaplan, M. A., and Feinberg, S. M. Potassium Salts in the Treatment of Pollinosis, *J A M A* **114** 2359 (June 15) 1940.

69 Miller, H., and Piness, G. Potassium Salts in Hay Fever, *J A M A* **114** 1627 (April 27) 1940.

70 Spain, W. C., Westcott, F. H., and Gaillard, G. E. Use of Potassium Chloride in the Treatment of Allergic Conditions, *J Allergy* **11** 388, 1940.

HAY FEVER

Several new pollen surveys are reported one from Manitoba by Walton and Dudley,⁷¹ one from Hawaii by Roddis,⁷² one from Brazil by Tupynamba and Oliveira Lima⁷³ and one from Tokyo and Kobe by Hara⁷⁴. The studies of Phillips¹¹ on the sugar beet, referred to previously, and the report of Swineford⁷⁵ on Catalpa pollen showed again how wide the possibilities of pollen implication may be.

Molds demand increased attention. In two papers, Pratt⁷⁶ has recently described his careful studies of the mold spore content in the air in Boston and New England and has pointed to marked improvement in his patients after mold extracts were included in their treatment. From Cuba comes a good paper by Cadrecha Alvarez and Quintero Fossas⁷⁷ describing the relation of the mold spore content in the air to changes in the barometer, in the wind velocity and in the temperature. The photographs in this article are handsome.

At the meeting of the Association for the Study of Allergy, held in New York in June 1940, Pennington⁷⁸ added the reports of cases of several patients to the list of proved cases in which hay fever depended on molds. Her patients reacted when the molds were applied by spray or by dried powder as a direct test on the nasal and bronchial mucosa—an important demonstration.

Waldbott and Ascher⁷⁹ point to the importance of rust and smut, the common parasites of grain which produce spores in enormous quantity, to cause trouble in almost 20 per cent of their patients. The his-

71 Walton, C. H. A., and Dudley, M. G. Pollen Survey in Manitoba, *Canad. M. A. J.* **42**:430, 1940.

72 Roddis, L. H. Pollens of Hawaii. Botanical Characteristics in Relation to Allergy, *U. S. Nav. M. Bull.* **38**:206, 1940.

73 Tupynamba, A., and Oliveira Lima, A. Pollinosis in Brazil, *Brasil-med.* **54**:185, 1940.

74 Hara, H. J. Hay Fever Among Japanese. Studies in Atmospheric Pollen in Tokyo and Kobe, *Arch. Otolaryng.* **30**:525 (Oct.) 1939.

75 Swineford, O., Jr. Catalpa as a Cause of Hay Fever. Case Report and Results of Eighty-Four Skin Tests, *J. Allergy* **11**:398, 1940.

76 Pratt, H. N. Mold Spore Content of the Air in Boston, with Reference to Atopic Sensitivity, *J. Pediat.* **14**:234, 1939; Seasonal Aspects of Asthma and Hay Fever in New England with Special Reference to Sensitivity to Mold Spores, *New England J. Med.* **219**:782, 1938.

77 Cadrecha Alvarez, J., and Quintero Fossas, J. M. Investigations Demonstrating Hourly Variations of Air-Borne Fungi in Relation to Meteorologic Influences, *Rev. de med. y cir., Habana* **44**:411, 1939.

78 Pennington, E. S. A Study of Clinical Sensitivity to Air Borne Molds, read at the Annual Meeting of the Society for the Study of Allergy, New York, June 11, 1940.

79 Waldbott, G. L., and Ascher, M. S. Rust and Smut. Major Causes of Respiratory Allergy, *Ann. Int. Med.* **14**:215, 1940.

tories of these patients corresponded well with the incidence of rust and smut spores in the air, their cutaneous reactions were often strongly positive, and when treatment with fungus extracts was combined with treatment with pollen extracts the results were good. Wittich⁸⁰ also has recognized the importance of grain smut and has found that in the grain belt section of the country the spores are more numerous than the pollens. His experiment, which could show a close immunologic relationship between the dusts of wheat mills and wheat smut, is interesting, for it suggests that wheat dust is often contaminated with the fungus.

Aside from the pollens and molds, there are other seasonal causes of trouble in patients with hay fever. Parlato⁸¹ was the first to call attention to the dust given off by caddis flies, which sometimes occur in enormous numbers along the southern shore of the Great Lakes. Now, Figley⁸² comments on the importance of May flies, which he finds in the country south of Lake Ontario. However, one must note that these flies must occur in tremendous numbers to cause trouble and so be fairly obvious. Prince⁸³ has a good paper on nonpollen factors simulating seasonal allergy. He comments on the fact that many patients with hay fever are skin sensitive to house dust and to animal danders, as well as to such other things as orris and pyrethrum, in addition to the pollens. His paper reminds me of several patients whose hay fever was found to have a definite seasonal relationship. It occurred only in summer when these persons went away to the seashore and came in contact with some particular dust in their summer cottage. When these patients brought their city mattress and bedding to the cottage with them, the symptoms disappeared. Problems like this may be hard to solve, as is shown well by the study of Weil⁸⁴. He reports the cases of 47 patients whose hay fever, in Montgomery, Ala., each year began around May and lasted until October. Reactions to cutaneous, intra-dermal and ophthalmic tests with grasses and weeds were negative in all of the patients, tests with constituents of fertilizer and insecticide were made and the reactions were negative, and, finally, tests with dusts of various insects—flies, moths and butterflies—showed only occasional

80 Wittich, F. W. The Nature of Various Mill Dust Allergens, *Journal-Lancet* **60** 418, 1940.

81 Parlato, S. J. A Case of Coryza and Asthma Due to Sand Flies (Caddis Flies), *J. Allergy* **1** 35, 1929.

82 Figley, K. D. Mayfly (Ephemeroidea) Hypersensitivity, *J. Allergy* **11** 376, 1940.

83 Prince, H. E. Nonpollen Factors Simulating Seasonal Respiratory Allergy, *South M. J.* **32** 956, 1939.

84 Weil, C. K. Summer Hay Fever of Unknown Origin in the Southeast, *J. Allergy* **11** 361, 1940.

positive reactions Two of the reactions to intradermal tests with molds were positive In his conclusion, the author states that the cause of this type of seasonal hay fever is unknown but that further study of the pecan scab and of the citrus white fly seems to offer the possibility of a solution to the problem

Studies on the mechanism of hay fever and its treatment begin with the pollen extract When pollen is extracted with a saline solution in the "regular way," examination of the pollen grain after the process shows little change in its size or contour, and the fact suggests that the active principle is either something which washes off the surface or something which dialyzes through the pollen cell membrane Reports have now been made on the effect of grinding the pollen in a ball mill Eagle and others,⁸⁵ of Johns Hopkins Hospital, ground ragweed pollen to a homogenous, creamy suspension but could observe no change in the immunologic character of the material, and at the end of the process the total nitrogen in the resulting extract gave a figure of 0.09 mg per cubic centimeter, which compares with 0.08 mg for the regular extract

Langner and Kein,⁸⁶ on the other hand, found that the yield of both total and protein nitrogen from ragweed pollen was consistently greater after defatting and grinding They likewise found no evidence of any qualitative difference among five extracts of ragweed pollen, each prepared in a different way

Stull and his associates⁸⁷ made an experimental study of pollen extracts modified by formalization, heating, radiation with ultraviolet light, acetylation and, finally, alum precipitation but found no essential difference between them The serologic effects of treatment seem to be demonstrated best when the simple fresh extract is used as the antigen

There appear to be two antibodies concerned with the mechanism of hay fever When the serum of a ragweed-sensitive patient is injected into the skin of a normal recipient, the reaction which takes place when the passively sensitized site on the skin is tested with ragweed pollen demonstrates the presence of a skin-sensitizing antibody in the patient This antibody is thermostable The serum which contains it can be inactivated by heating to 56 C and can be preserved for long periods in the ice box without losing its transferring ability The amount of anti-

85 Eagle, H , Arbesman, C , and Winkenwerder, W L The Use of the Low Temperature Ball Mill for the Preparation of Pollen Extracts, *Bull Johns Hopkins Hosp* 65 283, 1940

86 Langner, P H , and Kern, R A Studies in Extracts Made from Pollens Ground in a Ball Mill, *J Allergy* 11:488, 1940

87 Stull, A , Cooke, R A , Sherman, W B ; Hebard, S , and Hampton, S . Experimental Study of Fresh and Modified Pollen Extracts, *J Allergy* 11:439, 1940

body appears to be relatively constant in the same patient. It changes little as a result of specific treatment, regardless of whether the results of this treatment are good or bad.

In 1935, Cooke, Barnard, Hebal and Stull⁸⁸ demonstrated a second antibody. They found that if the original sensitizing serum was mixed with ragweed in a test tube and then incubated at 37 C for several hours, the skin-sensitizing antibody was neutralized by the added ragweed. Injections of the mixture into normal skin no longer prepared the site for reactions to further tests with ragweed. After treatment, however, this neutralization did not take place, and the skin-sensitizing antibody exerted its former effect, it was no longer neutralized by the ragweed added to it in the test tube, and the theory was that a new substance had blocked the combination between the ragweed and the skin-sensitizing factor. The study has been continued. This year, Sherman, Stull and Cooke⁸⁹ report the changes which are observed in patients treated over a period of years. The reactions to cutaneous tests are unchanged, the skin-sensitizing antibody increases at first and then seems to fall away, until after ten years 7 of 29 serums no longer sensitize passively. Likewise, the so-called blocking antibody increases at first, and then, as successful treatment continues, it seems to decrease. The changes, however, are not absolute and are not always parallel with the clinical results. Loveless⁹⁰ points out that whereas the skin-sensitizing antibody, or the so-called reagin, is somewhat thermolabile (being destroyed by heating to a temperature of 56 C for two hours), the blocking antibody is stable (resisting heating to 56 C for five hours), and so she is able to distinguish between the functions of the two. The blocking or inhibiting antibody develops after treatment, not only in patients with hay fever but in normal persons as well, and she implies that its presence is concerned with the good results obtained. These studies of antibodies give irregular results, no doubt, because the antigens used are not pure substances. At the last meeting of the Society for the Study of Asthma, Stull reported the presence of two different antigenic substances in ragweed, saying that some patients were more sensitive to one of these than to the other and that the blocking antibody was often directed more to one antigen than to the other. When all of the several active substances in ragweed can be isolated and identified, then

88 Cooke, R. A., Barnard, J. H., Hebal, S., and Stull, A. Serological Evidence of Immunity with Coexisting Sensitization in a Type of Human Allergy (Hay Fever), *J. Exper. Med.* **62** 733, 1935.

89 Sherman, W. B., Stull, A., and Cooke, R. A. Serologic Changes in Hay Fever Cases Treated Over a Period of Years, *J. Allergy* **11** 225, 1940.

90 Loveless, M. Immunological Studies of Pollinosis. I. The Presence of Two Antibodies Related to the Same Pollen Antigen in the Serum of Treated Hay Fever Patients, *J. Immunol.* **38** 25, 1940.

studies on antibodies to reveal the mechanism of hay fever and the mechanism of treatment will be satisfactory. It is not surprising that the results presented so far are hard to interpret.

Treatment of hay fever by feeding pollen by mouth would be extremely useful if it worked well. Schwartz⁹¹ reports the cases of 65 patients, of whom 40 per cent had obtained complete relief and another 47 per cent had satisfactory results from oral pollen therapy. Alperstein⁹² sought for the presence of ragweed pollen in urine and blood by testing the skin of sensitive patients with these fluids and found that when the pollen was given orally, an appreciable amount was absorbed through the gastrointestinal tract. The results of oral treatment in his hands were good.

This year, S. Feinberg invited workers in other clinics to cooperate in a comprehensive study of the results of treating hay fever by giving pollen by mouth.⁹³ The technic of treatment varied to some extent, but the results varied much more. In the series of cases reported from the University of Illinois College of Medicine good results were obtained in 26.8 per cent of 71 cases, in the series from Rush Medical College, in 25 per cent of 32 cases, and in the series from Northwestern Medical School and the University of Michigan Medical School, in 14.8 per cent of 27 cases. There were good results in a total of 29.8 per cent of the 141 cases in which treatment was given. And now comes an extraordinary finding illustrating once again the value of control. When in a small group of 32 cases treatment was administered in an entirely similar way but with capsules containing nothing but starch, good results were obtained with this placebo in 21.9 per cent. The authors drew two conclusions. First, opinion on the value of oral pollen therapy varies from complete rejection to limited acceptance, second, the effect is definitely inferior to that of parenteral injection of pollen extract. The article contains a number of interesting statistics, as well as important clinical observations.

SENSITIVITY TO MISCELLANEOUS ODD SUBSTANCES

This subject is often of considerable practical importance. Diodrast is sometimes injected intravenously to provide a contrast medium in roentgen studies of the renal pelvis. Last year, Crane⁹⁴ reported 5

91 Schwartz, S. C. Oral Pollen Therapy, *J. Lab. & Clin. Med.* **25** 566, 1940.

92 Alperstein, B. B. Oral Versus Parenteral Pollen Therapy, *J. Allergy* **11** 498, 1940.

93 Feinberg, S. M., Foran, F. L., Lichtenstein, M. R., Padnos, E., Rappaport, B. Z., Sheldon, J., and Zeller, M. Oral Pollen Therapy in Ragweed Pollinosis, *J. A. M. A.* **115** 23 (July 6) 1940.

94 Crane, J. J. Sudden Death Following Intravenous Administration of Diodrast for Intravenous Urography, *J. Urol.* **42** 745, 1939.

cases in which death occurred after the injection, and now Dolan⁹⁵ adds a sixth case. A woman of 65, subject to asthma for twenty years, was given 3 cc of diodrast intravenously and almost at once became cyanotic and apneic. She died in two minutes. The important point of the paper is the description of a simple test for sensitivity. The author suggests if 1 or 2 cc of the solution can be held in the mouth for a minute or two, sensitivity will be revealed promptly by marked swelling of the mucous membrane.

Hypersensitiveness to pituitary extract is reported by McMann⁹⁶. Insulin sometimes causes trouble, and now comes a report by Wasserman and his associates⁹⁷ to show that rabbits can be immunized to commercial insulin so that their blood serum will react with insulin to give a complement fixation. Incidentally, the specificity observed did not depend on the animal protein from which the preparation was derived. The report shows that insulin is a protein to which hypersensitiveness can develop. That it does not cause more trouble is probably explained by its use in small doses one or several times each day, which should desensitize the patient. Severe reactions to insect bites are described in an excellent paper by Benson⁹⁸. He found that extracts of bee's body caused a reaction which was quite as strong as that of the stinging mechanism itself. The antigen is dialyzable, it is thermostable, and it is species specific and perhaps order specific. Treatment with the extract is often effective. Chernay and his associates⁹⁹ declare that certain patients unusually sensitive to flea bites can be successfully desensitized with the corresponding extract.

House dust is of considerable practical importance, and much literature has developed about it. Hampton and Stull¹⁰⁰ made careful comparative studies of dusts from four different sources. Guinea pigs were sensitized to each of the four house dust extracts and then were tested in various ways. Three out of 10 guinea pigs reacted to dog hair extract, and 6 out of 8 reacted to feathers. So far, however, no substance has been found which would react invariably in animals sensitized with house dust. Each of three dusts neutralized to other dusts, and so the

95 Dolan, L. P. Allergic Death Due to Intravenous Use of Diodrast. Suggestions for Possible Prevention, *J. A. M. A.* **114** 138 (Jan 13) 1940.

96 McMann, W. Hypersensitivity to Solution of Posterior Pituitary, *J. A. M. A.* **113** 1488 (Oct 14) 1939.

97 Wasserman, P., Broh-Kahn, R. H., and Mirsky, I. A. Antigenic Property of Insulin, *J. Immunol.* **38** 213, 1940.

98 Benson, R. L. Diagnosis of Hypersensitiveness to the Bee and to the Mosquito, with Report on Successful Specific Treatment, *Arch. Int. Med.* **64** 1306 (Dec) 1939.

99 Chernay, L. A., Wheeler, C. M., and Reed, A. Flea-Antigen in Prevention of Flea Bites, *Am. J. Trop. Med.* **19** 237, 1939.

100 Hampton, S. F., and Stull, A. Antigenic Studies by the Dale Test. The Antigenicity of House Dust, *J. Allergy* **11** 109, 1940.

authors conclude that house dust contains some substance the nature of which is quite unknown but which, nevertheless, appears to be specific and characteristic of house dust Coulson and Stevens¹⁰¹ studied the relationship between dusts of various sorts and cotton linters and found that there was often a common antigenic relation

Cottonseed sensitiveness is not common, but when it occurs, the reactions to the ordinary watery cottonseed extract are violent and passive transfer to the skin of normal recipients often results in the demonstration of huge passive transfer reactions Bernton, Spies and Stevens¹⁰² observed 5 typical patients sensitive to cottonseed and found that in spite of a positive reaction to the cutaneous test, cottonseed oil applied to the nose and mouth caused no particular trouble and that the patients could eat cottonseed in the form of commercial shortenings (cottonseed oil or hydrogenated cottonseed oil) without difficulty In considering this paper, however, several discussers did not agree that the cottonseed oil was always harmless, saying that in several of their patients such symptoms as abdominal discomfort, canker sores and edema of the mouth developed when shortening made of cottonseed oil was used

The antigenic relationship among the members of certain food groups has been investigated Withers¹⁰³ made studies of vegetables and cereals and Tuft and Blumstein¹⁰⁴ of shellfish Piness and his associates¹⁰⁵ present a statistical study of tests with related and unrelated foods

"ECZEMA" AND CONTACT DERMATITIS

Landsteiner¹⁰⁶ has continued his studies on sensitization with simple chemical compounds and now, with an associate, describes the technic by which sensitiveness of the skin can be produced by the intraperitoneal injection of picryl chloride, the trick being to mix the chemical with killed tubercle bacilli suspended in paraffin oil and to inject the two

101 Coulson, E J, and Stevens, H Antigenic Relationship of Cotton Linters, Dust and Dust Precursors, *J Allergy* **11**:537, 1940

102 Bernton, H S, Spies, J R, and Stevens H Significance of Cottonseed Sensitiveness, *J Allergy* **11** 138, 1940

103 Withers, O R Food Allergens Atopic Reagents and the Botanical Classification of Foods, *J Allergy* **10** 105, 1939

104 Tuft, L, and Blumstein, G Studies in Food Allergy Antigenic Relationship of Shellfish, *J Allergy* **11**:475, 1940

105. Piness, G, Miller, H M, Carnahan, H D, Altose, A R, and Hawes, R C Relationship Between Foods as Shown by Skin Tests in One Thousand Children Under Thirteen Some Characteristics of the Skin Test, *J Allergy* **11** 251, 1940

106 Landsteiner, K, and Chase, M W Studies on the Sensitization of Animals with Simple Chemical Compounds Skin Sensitization by Intraperitoneal Injections, *J Exper Med* **71** 237, 1940

materials together. The considerable local reaction in the peritoneum enhances the absorption of the chemical substance.

Karaya gum is one of those insidious, little suspected substances which may cause much trouble, especially dermatitis, when sensitiveness to it develops. It occurs in cosmetics (especially hair-setting fluid), in certain foods, in pastes, in patent medicines and in certain industrial materials. Cases of hypersensitivity to it are reported by Feinberg and Schoenkerman¹⁰⁷ and by Figley,¹⁰⁸ who reviewed the literature. A host of other substances may cause similar trouble but only in those patients in whom there is a tendency for sensitiveness to these substances to develop. The "allergic constitution" is always important in evaluating any legal claims for injury, as was discussed in my review in the ARCHIVES last year.

Each year comes a new list of substances which have been identified as existing causes. The following selections are typical. Cheilitis from the tetrabromfluorescein in lipstick is reported by Hecht and others,¹⁰⁹ dermatitis from soap, by Jordon, Dolce and Osborne,¹¹⁰ and dermatitis from opium derivatives, in 3 nurses and a druggist, by Jordon and Osborne.¹¹¹ Schwartz and his associates¹¹² present an interesting and comprehensive paper describing an outbreak of dermatitis from the new resin fabric finishes which are found in the new wearing apparel devised in the frantic search for substitutes in this modern world. Still other and newer sources of danger may be expected at any time. Those interested in this subject will find much helpful information in a new textbook on occupational diseases of the skin by Schwartz and Tulipan.¹¹³

Norwood and Evans¹¹⁴ review 20 cases of eczematoid lesions of the hands which were found to depend on a fungus infection of the skin,

107 Feinberg, S. M., and Schoenkerman, B. B. Karaya and Related Gums as Causes of Atopy, *Wisconsin M. J.* **39** 701, 1940, abstracted, *J. A. M. A.* **115** 1491 (Oct. 26) 1940.

108 Figley, K. D. Karaya Gum (Indian Gum) Hypersensitivity, *J. A. M. A.* **114** 747 (March 2) 1940, correction, *ibid.* **114** 1091 (March 26) 1940.

109 Hecht, R., Rappaport, B. Z., and Bloch, L. Cheilitis, Fixed Drug Eruption and Gastro-Intestinal Allergy from Eosin Dye of Lipstick, *J. A. M. A.* **113** 2410 (Dec. 30) 1939.

110 Jordon, J. W., Dolce, F. A., and Osborne, E. D. Dermatitis of the Hands in Housewives. Role of Soaps in Its Etiology and Methods for Its Prevention, *J. A. M. A.* **115** 1001 (Sept. 21) 1940.

111 Jordon, J. W., and Osborne, E. D. Contact Dermatitis from Opium Derivatives, *J. A. M. A.* **113** 2075 (Nov. 25) 1939.

112 Schwartz, L., Spolyar, L. W., Gastineau, F. M., Dalton, J. E., Loveman, A. B., Sulzberger, M. B., Cope, E. P., and Baer, R. L. An Outbreak of Dermatitis from New Resin Fabric Finishes, *J. A. M. A.* **115** 906 (Sept. 14) 1940.

113 Schwartz, L., and Tulipan, L. *A Text-Book of Occupational Diseases of the Skin*, Philadelphia, Lea & Febiger, 1939.

114 Norwood, W. D., and Evans, E. E. Industrial Dermatitis from Gloves, *J. A. M. A.* **114** 1523 (April 20) 1940.

made worse by the macerating effect of the leather gloves which had to be worn in the industry And so it goes Sherlock Holmes can have no rest when he studies allergy

ASTHMA

Since allergy as a problem in immunology has been recognized as a study quite distinct from asthma as a problem in physiology, one's point of view has been broadened "All is not allergy that wheezes," and the statement is confirmed by a number of new clinical observations Overholt and Rumel¹¹⁵ analyzed 68 cases of primary carcinoma of the lung Cough, fever, pain, hemoptysis and loss of weight were the cardinal symptoms, but dyspnea occurred in 31 per cent and asthma in 73 per cent of cases Prickman and Moersch¹¹⁶ lay stress on the incidence and importance of bronchostenosis, which they found in 60 of 140 patients with asthma who were examined with the bronchoscope The stenosis should result in collapse of a portion of the lung, displacing the heart and elevating the diaphragm toward the lesion It could be mistaken for pneumonia However, in 43 per cent of their patients the roentgenogram showed nothing abnormal When stenosis was found, the bronchus was dilated with special forceps introduced through the bronchoscope, and great relief of the asthma was obtained In most cases the trouble was caused by infection of the wall, but in certain cases they found it was due to cancer or to tuberculosis or even to the ulceration of calcareous material from a lymph node through the bronchial wall Goodyear¹¹⁷ had a case of asthma in a child in which he found that the symptom was due not to allergy but to an open safety pin in the throat

That a spasm of the pulmonary blood vessels may cause asthma is suggested by Kuhlmann¹¹⁸ In a roentgen study of the chest of a patient undergoing a severe attack of asthma, he observed that the upper part of the left lung was quite free of vascular markings, and after exclusion of pneumothorax, he concluded that complete collapse of the local blood vessels was responsible for the lack of normal shadows The thought fits in with the suggestion made by an associate and me¹¹⁹ and with

115 Overholt, R H, and Rumel, W R Clinical Studies of Primary Carcinoma of the Lung, *J A M A* **114** 735 (March 2) 1940

116 Prickman, L E, and Moersch, H J Bronchostenosis Complicating Allergic and Infectious Asthma, *Ann Int Med* **14**:387, 1940

117 Goodyear, H M Suspected Allergy Bronchial Asthma, Open Safety Pin Found at Time of Adenoid Operation, *J Med* **21** 172, 1940

118 Kuhlmann, F Blood Vessel Occlusion in Bronchial Asthma, *Deutsche med Wchnschr* **65** 833, 1939

119 Rackemann, F M, and Greene, J E Periarteritis Nodosa, *Tr A Am Physicians* **54** 112, 1939

that of Harkavy¹²⁰ that vascular lesions may play a part in some types of asthma

Asthmatic bronchitis has been described by me¹²¹ as indicating wheezy colds occurring only two or three times a year without evidence of new contacts with new environmental dusts and with entirely free periods between the attacks, but the term is used now by Bivings¹²² to describe a much more chronic respiratory disturbance in children. The patients have a cough, anemia, a slight fever and generalized pains. Reactions to tuberculin tests are negative, but roentgen examination of the lungs may show localized infiltration, especially in the lower lobes. Treatment is largely symptomatic but includes vaccines. Watson the Doctor may be even more important than Holmes the Detective!

The immediate treatment of an attack of asthma is better understood each year. In the clinic at the Massachusetts General Hospital, my associates and I have adopted the slogan "treat them gently." By this is meant that a patient should be protected in every way, not only from the dust in his environment and from sudden changes in temperature, but, more important, from those drugs which might make his asthma worse instead of better.

Drug allergy is always important. It occurs when least expected, and it may lead to serious trouble. A middle-aged woman came into the hospital for bronchoscopic examination and before the operation was given 0.25 grain (0.015 Gm.) of morphine sulfate and 1.5 grains (0.095 Gm.) of phenobarbital. She stood the operation well and appeared comfortable throughout the trying procedure, but on return to the ward, her condition rapidly became worse, violent asthma developed and she became cyanotic and almost died. It was with difficulty, and only with the aid of oxygen and the intravenous injection of saline solution, that she recovered. Her convalescence lasted five weeks. About a year later, the same woman came again for another bronchoscopic examination. This time she was taken to the operating room without previous medication of any kind. The passage of the bronchoscope was not pleasant, but she stood the procedure well, and this time she returned to the ward in good condition, the next day her asthma was much better, instead of much worse. Her stay in the hospital lasted five days, instead of five weeks.

We "treat them gently" chiefly by withholding all drugs except those with simple chemical formulas, including chloral hydrate, paralde-

120 Harkavy, J. Vascular Allergy in the Pathogenesis of Bronchial Asthma with Recurrent Pulmonary Infiltration and Eosinophilic Polyserositis, *J. Allergy* **11** 622, 1940.

121 Rackemann, F. M. Intrinsic Asthma, *J. Allergy* **11** 147, 1940.

122 Bivings, L. Asthmatic Bronchitis Following Chronic Upper Respiratory Infection, *J. A. M. A.* **115** 1434 (Oct. 26) 1940.

hyde and such simple salts as bromides, iodides and saline laxatives. If the asthma is severe, food is withheld for twenty-four to forty-eight hours, but fluids are forced as "liquids without milk." If these fluids are not taken well by mouth, they are given intravenously as a physiologic solution of sodium chloride usually containing 5 per cent dextrose, and to the flask may be added 1 cc of a 1 to 1,000 dilution of epinephrine hydrochloride, with thorough stirring, so as to produce a dilution of 1 part of epinephrine hydrochloride in 1,000,000 parts of solution. Under this treatment, most patients recover with fair rapidity. We are convinced that gentle treatment is worth while.

Powdered epinephrine base suspended in oil is useful, as attested in a new paper by Keeney,¹²³ but there are several reports of disagreeable reactions following its use. Dorwart¹²⁴ reports the case of a woman aged 22 who was given 0.3 cc of a 1 to 1,000 aqueous solution of epinephrine hydrochloride and at the same time 1 cc of a suspension of powdered epinephrine base in oil. Soon came shaking, pallor, twitching and cyanosis, with a pulse rate of 160, to make a desperate picture, which lasted for about five hours.

Maietta¹²⁵ describes 2 cases. One was that of a man of 37 who had had asthma for eighteen years. After an intramuscular injection of a suspension of powdered epinephrine base in oil, he, too, had a reaction, with chills, cold hands and feet, sweating, headache, pallor and palpitation—characteristics of shock. The other case was that of a woman of 38 who was given 0.4 cc of an aqueous solution of epinephrine hydrochloride in one arm and 1 cc of a suspension of powdered epinephrine base in oil in the other arm. Within an hour there was blanching at the site of the injection of oil, with redness, which extended from her shoulder to her wrist, marked edema, induration and pain, this local reaction lasted for six days. Keeney himself¹²⁶ reviews the reactions which may occur.

For some years, Barach¹²⁷ has advocated the use of helium in a mixture containing 80 per cent of this low gravity gas and 20 per cent of oxygen. In my experience, however, 100 per cent oxygen is better, and the technic which Boothby and his associates¹²⁸ describe is satis-

123 Keeney, E. L. Epinephrine in Oil. Its Effectiveness in the Symptomatic Treatment of Bronchial Asthma, *Am J M Sc* **198**:815, 1939.

124 Dorwart, F. G. "Slow Epinephrine." An Experience, *J A M A* **114**:647 (Feb 24) 1940.

125 Maietta, A. L. Systemic and Local Reactions to Epinephrine in Oil, *New England J Med* **222** 715, 1940.

126 Keeney, E. L. Reactions of Epinephrine in Oil, *J A M A* **114**:1098 (March 23) 1940.

127 Barach, A. L. Use of Helium as a New Therapeutic Gas, *Proc Soc Exper Biol & Med* **32** 462, 1934.

128 Boothby, W. M., Mayo, C. W., and Lovelace, W. R. One Hundred Per Cent Oxygen, *J A M A* **113** 477 (Aug 5) 1939.

factory The use of epinephrine hydrochloride in a strong 1 to 100 dilution to be inhaled as a spray was first advocated by Graeser and Rowe¹²⁹ in 1935, and a modification of it consists in adding a 0.5 per cent solution of chlorobutanol, which makes a more powerful and more penetrating medicated spray, according to Richards, Barach and Cromwell¹³⁰ These authors have suggested the device by which a hand atomizer is attached to a tank of straight oxygen, so that the spray becomes not only strong but continuous and may be used for as long as ten minutes at a time The results are said to be good

Sulfanilamide has been advocated, as might be expected, and no doubt other reports will appear in the near future Weil and Climo¹³¹ obtained relief in 6 out of 7 cases of status asthmaticus by the use of sulfanilamide Bruhl¹³² uses insulin and speaks of an "insulin thrust," which results in leukocytosis, an increase in blood pressure and a decrease in temperature, the opposite of the so-called Widal's hemoclastic crisis, which was supposed to be typical of allergic reactions I have had no experience with insulin

Theophylline with ethylene diamine, also called "aminophylline," was first used in the treatment of asthma by van Leeuwen in 1932, but little attention was paid to it until 1935, when Tuft¹³³ read a paper on the use of drugs in allergy and recommended further trial of it Since then, theophylline with ethylene diamine has been used in many clinics and found to be useful, especially for those patients with severe asthma who do not respond well to epinephrine A new paper on the subject is that by Efron and Everett¹³⁴

During the year, every one has learned a little and the management of patients with hay fever, with dermatitis and with asthma has improved in many of its details The fundamental nature of allergy remains obscure The field is large, and it is spread wide for some brilliant investigator to show how it can be cultivated to produce a rich harvest which is badly needed and the seed from which, once started, will grow exceedingly

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129 Graeser, J. B., and Rowe, A. H. Inhalation of Epinephrine for the Relief of Asthmatic Symptoms, *J. Allergy* **6** 415, 1935

130 Richards, D. W., Jr. Barach, A. L., and Cromwell, H. A. Use of Vaporized Bronchodilator Solution in Asthma and Emphysema. A Continuous Inhalation Method for Severe Asthmatic States, *Am. J. M. Sc.* **199** 225, 1940

131 Weil, C. K., and Climo, H. J. Status Asthmaticus. Specific Chemotherapy in Treatment, *Alabama M. A. J.* **9** 370, 1940

132 Bruhl, W. Antiallergic Action of Insulin, *Klin. Wchnschr.* **18** 1541, 1939, abstracted, *J. A. M. A.* **114** 1414 (April 6) 1940

133 Tuft, L., and Brodsky, M. L. The Influence of Various Drugs upon Allergic Reactions, *J. Allergy* **7** 238, 1936

134 Efron, B. G., and Everett, P. Theophylline Ethylenediamine (Aminophyllin) in Bronchial Asthma, *New Orleans M. & S. J.* **92** 77, 1939

Book Reviews

Reflektorische und algetische Krankheitszeichen der inneren Organe By Prof Dr K Hansen and Dr H von Staa, Lubeck Price, 28 marks Pp 270 Leipzig Georg Thieme, 1938

Hansen and von Staa believe that diseases invading internal organs frequently set in motion certain nervously excited reflexes, detection of which would aid in the recognition of the maladies initiating such reflexes. The signs are usually unilateral and are homolateral to the organs affected.

"Sympathetic anisocoria," the sympathetic difference in pupillary equality, is the point of origin for the investigation as reported by the authors in this volume. This pupillary enlargement, pointing a diagnostic finger to an ipsilateral organ disease, if it is accompanied by other unilateral reflex phenomena, may in their opinion offer valuable aid in indicating the affected organ.

A chapter is devoted to a historical introduction to the problem of reflex and algetic signs of disease. The importance of the observations of MacKenzie and Head is discussed. The work of Head is reviewed at some length. Head, it is noted, pointed out that diseases of certain organs set up sensory hyperirritability in definitely localizable regions of skin. He demonstrated that hyperalgetic cutaneous zones (Head zones) possess a definite order for individual visceral diseases. Definite zones are assigned to definite organs, and this phenomenon, which was originally discovered empirically, is founded in the metameric construction of the organism, the consequent law of segmental innervation. The authors believe that hyperalgetic cutaneous zones as well as vegetative, motor and sensory innervation of a visceral organ are coordinated by the same spinal segment. The contribution of Knotz was the demonstration that the reflex signs of disease of the internal organs are unilateral, occurring on the same side as the organ involved, furthermore, he pointed out the diagnostic importance in the recognition that these various phenomena correspond segmentally to the organ responsible for their origin.

In chapter 3 are outlined in detail the various asymmetric phenomena which may arise as reflexes from diseased organs. The authors consider first "sympathetic anisocoria." The diameter of the pupil homolateral to the diseased organ is increased. The authors believe that this increase is one of the most common of the reflexes, but they point out that this may be important only if it is associated with other reflex phenomena. In the presence of an enlarged pupil there is usually a slight protrusion of the ocular bulb, resulting in a widened palpebral fissure. The eye is brighter because of increased lacrimation. Frequently, inspection of the patient will reveal a faint spasm of the facial muscles on the side corresponding to the pupillary enlargement. Observation of the patient's posture in the recumbent position often discloses the fact that certain muscle groups exert a unilateral protective contraction, causing the patient to keep his body in a bent position. Asymmetric motion of the thorax with respiration often can be detected in persons with pulmonary and pleural diseases, and not infrequently this can be demonstrated in association with abdominal illnesses. Unilateral facial herpes and herpes zoster, although less common, may be part of the reflex manifestation indicating disease of the internal organs. Various forms and degrees of localized muscle resistance are frequent accompaniments of such diseases. This resistance may be superficial, or it may involve the deep muscle layers of the thorax or abdominal wall. Usually, this resistance is unilateral and in nervous origin corresponds segmentally to the diseased organ. Vasomotor changes, such as local cyanosis or increased dermatographism, can be noted at times. These are said to correspond in nervous origin

segmentally and homolaterally to the organ affected. According to the authors, localized unilateral piloerector and anisohydrotic phenomena can at times result from sympathetic nervous excitation originating in a diseased organ.

Referred pain and tenderness are considered to be among the most frequent and important of the signs and symptoms of diseases invading the internal organs. By "referred" pain Hansen and von Staa mean not pain felt in the region of the disease process itself but that which is caused reflexly in secondary regions, these corresponding to the dermosensitive segmental regions corresponding to the organ involved. Hansen and von Staa divided these conditions into (1) superficial pain or cutaneous hyperalgesia, the so-called Head zones, and (2) deep pain or hyperalgesia of the deeper muscles, connective tissues and periosteum, the so-called MacKenzie zones. In addition to the unilateral manifestation already mentioned, the authors also describe so-called organ reflexes or viscerovisceral signs which affect neighboring or distantly situated organs. They refer to complications, such as vomiting, flatulency, headaches and intestinal, cardiac and genitourinary irregularities of various types, which not infrequently arise as reflexes of diseases invading the internal organs.

One hundred and twenty-seven pages of the book are devoted to a careful investigation of a number of patients with various diseases, to ascertain how frequently these reflex signs may be detectable and how useful their recognition may be in the diagnosis of such diseases. The number of patients with each type of disease, as well as the respective parts diseased, are given as follows: 90, lungs and pleura, 28, heart, 56, liver, gallbladder and biliary ducts, 7, pancreas, 47, stomach, 40, duodenum, 6, spleen, 9, descending portion of the colon and sigmoid flexure, 4, appendix, 2, ovary, 30, kidney, 9, head, and 10, extremities. On reviewing the results of the investigation, Hansen and von Staa tabulated their findings as follows: total number of cases, 338, incidence of unilateral pupillary enlargement, 86.9 per cent, incidence of increased palpebral fissure and increased brightness of one eye, 55.3 per cent, of spasm of facial muscles, 66.3 per cent, of herpes, 6.6 per cent, of vasomotor phenomena, 31.5 per cent, of piloerection, 12.3 per cent, of anisohydrosis, 3.8 per cent, of muscle spasm, 71.7 per cent, of deep hyperalgesia, 28.6 per cent, and of superficial hyperalgesia (Head zone), 23.2 per cent.

A review of their clinical experience leads Hansen and von Staa to draw the following five conclusions:

1. The reflex and algetic signs are practically always limited to one side, right or left, in the case of paired organs the syndrome is homolateral to the diseased organ, in the case of organs which are not paired, the syndrome is still unilateral, in a general way corresponding to the somatic position of the unpaired organ.

The position of the organ and its reflexly attributed signs are indicated as follows:

*Organs Producing
Reflex Signs on the Right*

Right lung
Right pleura
Pyloric portion of the stomach
(bulb, duodenum)
Ileum
Ascending colon
Liver
Gallbladder
Right kidney
Right ureter
Right testicle
Right ovary

*Organs Producing
Reflex Signs on the Left*

Left lung
Left pleura
Heart
Aorta
Cardiac portion of the stomach
(corpus, fundus)
Jejunum
Descending colon
Spleen
Pancreas
Left kidney
Left ureter
Left testicle
Left ovary

2 After a study of these signs has localized the disease to the right or the left side, the segmentally demarcated reflexes and algetic manifestations will point to the involvement of an internal organ occupying the corresponding segmental position, and this fact usually will enable the examiner to make rather accurate identification of the organ responsible for the reflexes

3 An increase in the extent of the projection of these unilateral or segmental signs of disease is always an indication of the spread of the disease or of secondary complications in other organs

4 The reflex symptoms referable to regions of pain in the head follow the unilateral rule but not the metameric principle (that is, the segmental distribution)

5 The special diagnostic value of the symptoms lies in the fact that they can be present in the absence of spontaneous pain. Diseases which may have caused pain but no longer produce it may still cause other of these reflex signs. Painful visceral diseases are always associated with reflex symptoms. Conversely, if pain is present and reflexes are absent, then the pain is caused not by visceral disease but by malingering, by hysteria or by some organic disease of the nervous system.

Two chapters of the book are devoted to a discussion of the anatomic and physiologic aspects of the reflex and algetic signs of disease. The authors go into great detail in analyzing mechanisms for the production of these signs and venture some definite impressions regarding the pathways utilized in their transmission.

The various phenomena described in this book are largely dependent on the sympathetic nervous system for origin or transmission. The authors seem to minimize the importance of the spinal sensory system of nerves as aids to the sympathetic nervous system in warning of organic disease. In all probability, the first line of defense for a diseased visceral organ is demonstrable in the sympathetic system of signal devices. When a spread of the disease occurs, however, such as would occur in the presence of a peptic ulcer which was proceeding to penetrate, thus invading neighboring tissues, contact would be made with spinal sensory nerves which supply the parietal peritoneum and actually come close to walls of the bowels over posterior abdominal wall appendages. The better differentiating peripheral portions of these nerves over thorax and abdomen may then be utilized in painful expressions to indicate that an emergency is arising.

At the Mayo Clinic such shift of pain into secondary regions has been found to occur in more than 90 per cent of cases in which ulcers were present, when the ulcers exhibited definite penetrating characteristics. The reflex phenomena described in this book may develop into useful aids in differentiating pain originating in visceral organs from that type of pain having its origin in the somatic system. It is possible that murally arising pains utilizing spinal sensory nerves can be identified through the absence of the reflex signs described by the authors. At the clinic studies are at present being carried on in an attempt to corroborate or disprove such a hypothesis.

Although the reader may not agree with all the authors' conclusions, a reading of this book will have its reward in increased knowledge of the nervous system and in a keener interest in the various phenomena which may arise as indications of organic disease. The book represents a tremendous amount of painstaking work, it is well written and attractively edited. It is well worth careful study.

An Introduction to Gastro-Enterology By Walter C. Alvarez, M.D., Professor of Medicine, University of Minnesota. Price, \$10. Pp. XXII + 778, with 186 illustrations. New York: Paul B. Hoeber, Inc., 1940.

In 1922 there appeared an unassuming book called "The Mechanics of the Digestive Tract." It was 200 pages long, had 22 illustrations and a bibliography of 456 references and sold for \$3.50. The *ARCHIVES OF INTERNAL MEDICINE* reviewed it (29:869-870 [June] 1922) and spoke well of it. Perhaps the author's views were a little too novel to suit the conservative taste of the *ARCHIVES*. But, on the other hand, the author knew how to write vigorously, had enthusiasm and obviously was a good clinician with excellent laboratory training and a scholarly

knowledge of medical literature. Thus it was said that the book was a valuable compilation, almost certain to interest physicians and physiologists. This was a good prophecy.

In 1928 the second edition made its appearance, still an unassuming book, with the same title, but now further qualified by being earmarked "An Introduction to Gastroenterology." It had grown considerably: the second edition was 447 pages long, had 100 illustrations and a bibliography of 900 references and sold for \$7.50. *The Journal of the American Medical Association* (91:420 [Aug. 11] 1928) reviewed it favorably. The review described the book as containing a fund of information and as being a most useful tool for those laboring in the field of digestive disorders.

Now the third edition appears, longer, more profusely illustrated than ever before and with a fine bibliography carefully selected from many references, the author modestly says this is probably the best part of the book. It sells at a price nearly three times what its grandfather cost. Since it has changed its name to "An Introduction to Gastro-Enterology," the fact that it is the third edition of "The Mechanics of the Digestive Tract" receives less emphasis. Thus, besides being bigger, better dressed and more prosperous, it has placed a hyphen in its title and has become a trifle highfalutin.

But all the same it is a fine book. The author has lost none of his vigorous enthusiasm since the first edition was written, and now he has developed added literary charm. The result is that he has produced a scholarly piece of work, in fact, just the kind of a volume which any one who wishes to be introduced to diseases of the stomach and intestines will appreciate. Besides being informative and authoritative, it is a joy to peruse. Pictures of pioneers in the building up of knowledge in gastroenterology constitute a commendable addition. The final chapter, on books and reading, is delightful.

Some of the older clinicians who admired so much the second edition, as they read of gastroscopy, of electrogastragrams and of tubes and balloons that explore the intestinal tract from roof to cellar, will again agree with Josh Billings and will regret that the third edition has omitted to quote those homely words of his which used to appear opposite the title page: "I hav finally kum tu the konklusjon that a good reliable sett ov bowels iz wurth more tu a man than enny quantity ov brains."

Physiological Chemistry By Albert P. Mathews, Professor of Biochemistry, University of Cincinnati. Sixth Edition. Price, \$8.00. Pp. 1,488. Illustrated. Baltimore: The Williams and Wilkins Company, 1939.

"The various objects on the surface of the earth may be divided into two great classes, the living and the non-living, the former being characterized by the possession of certain properties which the latter lack. The first of the distinctive properties of living matter is the power of movement, and of movement having an internal rather than an external origin. These movements are either from place to place, as in animals, or movements of growth and foliage as in plants. It is by the property of movement that we instinctively distinguish living and lifeless."

These sentences, introductory to chapter I of "Mr." Mathews' book—in former days he objected to Doctor or Professor—recall lectures and discussions which for this reviewer, as a beginning student of medicine, were vivid and memorable. Mathews then, in 1907, recently had been elevated to the chair of physiologic chemistry at the University of Chicago. Much that was hoped for at that time in the development of the biologic sciences now has been accomplished, and the new knowledge has contributed immensely to the science of medicine. The "art of medicine" Mathews would say was largely the art of guessing, "the art of guessing the name of the disease and of happy success or of dismal failure in prescribing remedies." An example of the greater certainty of today's medical knowledge may be cited.

"It was found by Buchner, in 1897, that if yeast be ground with sand mixed with diatomaceous earth, and then filtered by very high pressure in a hydraulic

press, the clear filtrate or pressed juice had the power of fermenting sugar. He attributed this power to an enzyme which he named *zymase*." In 1904 Harden and Young filtered *zymase* through gelatin and obtained two fractions. Neither fraction alone was active, but when they were reunited the fermentative power was restored. The fraction which filtered was named *cozymase*. For several years *cozymase* was believed to occur only in the lower plants, but in 1918 Meyerhof found it in mammalian tissue and thus could demonstrate "the essential identity of the fundamental chemical process in all living matter." When mammalian *cozymase* was added to the filtrable fraction of the *zymase* of yeast, the fermentative and respiratory activities were restored, and also when the *cozymase* of yeast was added to washed frog muscle, the power of respiration of the latter was restored. Mathews emphasizes that this is one of the most important discoveries of biochemistry. It also has been most fruitful for modern medicine, because nicotinic acid later was identified among the decomposition products of *cozymase*, which led naturally to recognition of the significance of nicotinic acid in the prevention of pellagra.

Whoever is seeking information about the more important present day knowledge of the properties of living objects on the surface of the earth and the chemical adventures of the constituents of living matter can begin no better than by reading this book. Nor will he be disappointed in the manner of presentation. A medical textbook, as has been said by the widely quoted Sir Robert Hutchison (*Lancet* **11** 1059-1062 [Nov 18] 1939), is usually arid and dusty as the Sahara, although the subject matter may be as exciting as "one of those omnibus volumes of detection mystery and horror." The requisites of readability demanded by Sir Robert are met by Mathews at every turn. For instance, in the summary of the subject of phosphoric acid esters of dextrose (page 102) we read "Phosphoric acid meets it [*glucose*] at the door [Mathews would probably resent editorial insistence on *dextrose*], extends to it a hand, is married to it by phosphatase (*cozymase*), that universal clergyman, and escorts it through the cell. Glucose is now embarked, in the company of this phosphoric acid, on that exciting series of adventures, breath taking, which it undergoes in living matter, and which leads finally to its complete undoing and ultimate resolution into the elements of carbonic acid and water from which it arose." The romance is all here, without sacrifice, in any way, of reality.

Pneumoconiosis (Silicosis) The Story of Dusty Lungs A Preliminary Report By L. G. Cole, M.D., Director of Silicotic Research, John B. Pierce Foundation, New York, and W. G. Cole, M.D. Price, \$1 Pp 52, with appendix. New York: John B. Pierce Foundation, 1940.

This monograph is attractively made. It gives the impression of having been written primarily for the benefit of its sponsor, the John B. Pierce Foundation. Whether this is true or not, the book gives a readable account of pneumoconiosis, understandable alike to layman and physician.

The cause of pneumoconiosis is discussed, as well as the pathogenesis and pathologic structure of the condition, the disease is considered as a clinical problem, as a social and economic problem and even as a medicolegal problem. There is an excellent chapter at the end on the roentgenology of the disorder, a little unconvincing, perhaps, as the authors admit, because of the absence of reproductions of roentgenograms.

The fault, however, is well compensated for in the appendix. Here are reprinted two strictly professional articles by the authors: one from *Radiology* (**33** 261-290 [Sept] 1939) on the roentgenologic diagnosis of pneumoconiosis and the other from *The Journal of the American Medical Association* (**113** 1216-1221 [Sept 23] 1939) on the dyspnea of silicosis. These two articles, of course, are authoritatively written and well illustrated.

The monograph is worth having in a medical library. Students, particularly, will appreciate it, for it clarifies the subject of pneumoconiosis in an altogether gratifying manner.

Electrocardiographic Patterns By Arlie R Barnes, M D Price \$5 Pp 197, with 94 illustrations Springfield, Ill Charles C Thomas, Publisher, 1940

With every new technical procedure, there is always the danger of reading too much or too little into it This monograph presents clearly the controversial issues of electrocardiography, and its bibliography is an excellent guide for more intensive reading The book should prove invaluable to the large group of internists who use the electrocardiograph in their daily work It is not a book for beginners But the persons who read electrocardiograms and who are puzzled by the diversity of patterns and by the "borderline" group will find it a helpful guide

The chapter on left and right strain is particularly arresting Time alone will determine the truth of Dr Barnes's view on this phase

When first introduced, the claims for the fourth lead made many men suspicious to the point of avoiding its use Dr Barnes's correlation of this lead with old standard leads is sound and refreshing The chapter on the various fourth leads is so "technical," however, that it is questionable whether the average internist will read it

The organization of the book and its illustrations are very pleasing and satisfactory Its efficiency and clearness are typical of the author and of the clinic of which he is a member Despite the author's use of the old fourth lead, the illustrations, the timeliness and the treatment of the subject give his book a distinctive place among the many books on electrocardiography

Illustrative Electrocardiography By Julius Burnstein, A B, M D Second edition Price, \$5 00 Pp 292 New York D Appleton-Century Company, Inc, 1940

As the name implies, this book consists of a series of graphic records of patients who have shown abnormal electrocardiograms They represent selections from over 7,500 persons The book is essentially one for the beginner A simple descriptive style has been followed throughout, so that the neophyte, starting with the first series of plates, which are normal ones and which show minimal changes in the several complexes, is able ultimately to come to the interpretation of difficult and unusual electrocardiograms

The book is printed on semiglossy paper, which makes for clarity of the tracings Unfortunately, but for obvious reasons, the length of the book is out of all proportion to its width, so that it cannot be kept in the ordinary library bookcase

The Care of a Small Rat Colony By Rolland J Main Price, \$2 00, cloth Pp 101, with illustrations St Louis C V Mosby Company, 1939

This little book should be of great value to any one interested in the maintenance of a small rat colony The author describes in considerable detail the problems encountered in regard to size, ventilation, temperature and humidity of the rat quarters The chapter on equipment gives in many instances the source of purchase and the price Rearing, mating, growth and feeding of rats are thoroughly discussed The author's method for the assay of vitamin D in milk is also included

Diagnostica differenziale delle emopatie By Edoardo Storti Pp 357 Milan Cromotipia E Sormani, 1939

This is an excellent publication, dealing with the diagnostic problems encountered in the study of blood dyscrasias The chapter on the differential diagnosis of splenomegaly offers one of the most complete discussions to be found on the subject The color plates are unusually good The pictures of the blood cells appear as exact reproductions of the originals and will serve as an excellent pictorial reference

CARDIAC LESIONS ASSOCIATED WITH CHRONIC INFECTIOUS ARTHRITIS

ARCHIE H BAGGENSTOSS, M D

AND

EDWARD F ROSENBERG, M D *

ROCHESTER, MINN

Opinions as to the presence and nature of cardiac lesions associated with chronic infectious (rheumatoid) arthritis have been varied Fuller¹ and Garrod² have stated that, as a rule, the heart is not injured in rheumatoid arthritis Fuller stated that he had never seen a case in which he could attribute pericarditis or endocarditis to rheumatoid arthritis Garrod observed that if patients with rheumatoid arthritis have valvular insufficiency, one can assume a previous attack of rheumatic fever has been the cause of the lesion

Strumpell³ and Pribram⁴ stated that in rheumatoid arthritis of slow, insidious onset cardiac involvement does not occur, but when the disease is ushered in by an acute febrile attack of arthritis the heart is often implicated

Barjon,⁵ on the other hand, estimated that the number of cardiac complications is just as high in the cases of rheumatoid arthritis with chronic onset as in those of acute polyarthritis at the onset

Clinical investigations of the heart in cases of chronic infectious arthritis have been reported by Bannatyne,⁶ Barjon,⁵ Pribram,⁴ McClae,⁷

* Fellow in Medicine, the Mayo Foundation

From the Section on Pathology, the Mayo Clinic (Dr Baggenstoss)

1 Fuller, cited by Pribram⁴

2 Garrod, A E A Treatise on Rheumatism and Rheumatoid Arthritis, London, Charles Griffin and Company, 1890, pp 261-263

3 Strumpell, A Lehrbuch der speciellen Pathologie und Therapie der inneren Krankheiten für Studierende und Aerzte, Leipzig, F C W Vogel, 1902, vol 3, pp 525-526

4 Pribram, A Chronischer Gelenkrheumatismus und Osteoarthritis deformans, in Nothnagel, H Specielle Pathologie und Therapie, Vienna, A Holder 1902, vol 7, pt 5, p 62

5 Barjon, cited by Boas and Rifkin⁸

Boas and Rifkin,⁸ Froggatt,⁹ Coates,¹⁰ Master and Jaffe,¹¹ Kahlmeter,¹² Monroe and Walcott,¹³ and Monroe¹⁴ According to these reports, the clinical incidence of cardiac lesions varies from 4 per cent (Coates and Monroe) to 40 per cent (Kahlmeter, for "secondary chronic arthritis")

The value of these clinical reports is limited because (1) the type of chronic arthritis studied is not always clearly defined, (2) clinical data (symptoms, signs, roentgenograms and electrocardiographic tracings) are often insufficient to make an accurate diagnosis of the nature or site of a cardiac lesion and (3) mild or healed cardiac lesions may give no clinical indication whatsoever of their presence

Pathologic studies of the heart in cases in which chronic infectious arthritis is known to have occurred during the life of the patient are few Charcot¹⁵ mentioned that there was pericarditis in 4 out of 9 cases of "chronic rheumatism" in which necropsy was performed Kast,¹⁶ in 1901, studied the postmortem incidence of cardiac lesions in cases in which "chronic rheumatism" of various types had occurred during life Of 13 cases of "primary chronic arthritis" (rheumatoid?), endocarditis occurred in 2, subacute pericarditis in 1 and obliteration of the pericardial sac in 1 In 3 of 4 cases of "secondary chronic arthritis," endocarditis

6 Bannatyne, G A Rheumatoid Arthritis Its Pathology, Morbid Anatomy and Treatment, ed 2, Bristol, John Wright and Company, 1898, pp 115-116

7 McCrae, T Arthritis Deformans, in Osler, W, and McCrae, T Modern Medicine Its Theory and Practice, ed 3, Philadelphia, Lea & Febiger, 1915, vol 5, pp 914-915

8 Boas, E P, and Rifkin, P The Heart in Arthritis Deformans, J A M A **82** 1596-1599 (May 17) 1924

9 Froggatt, T W Incidence of Heart Lesions in Infective Arthritis, Lancet **2** 116 (July 19) 1924

10 Coates, V The Kinship of Rheumatic Fever and Rheumatoid Arthritis, M J & Rec **133** 55-56 (Jan 21) 1931

11 Master, A M, and Jaffe, H Rheumatoid (Infectious) Arthritis and Acute Rheumatic Fever The Differential Diagnosis, J A M A **98** 881-882 (March 12) 1932

12 Kahlmeter, G De l'existence de lésions myocardiques et valvulaires dans les diverses formes de polyarthrites chroniques et des conclusions qu'on en peut tirer touchant l'étiologie et le groupement clinique des polyarthrites chroniques, Acta med Scandinav, 1934, supp 59, pp 611-625

13 Monroe, R T, and Walcott, C F The Incidence of Cardiovascular Disease in Chronic Arthritis, in Medical Papers Dedicated to Henry Asbury Christian, Physician and Teacher, in Honor of His Sixtieth Birthday, Baltimore, Waverly Press, Inc, 1936, pp 918-927

14 Monroe, R T Chronic Arthritis, in Christian, H A Oxford Medicine, New York, Oxford University Press, 1936, vol 4, pt 2, pp 307-404

15 Charcot, J M Clinical Lectures on Senile and Chronic Diseases, translated by W S Tuke, London, The New Sydenham Society, 1881, pp 172-175

16 Kast, L Ueber das Verhalten der Herzaffectationen bei chronischen Gelenkrheumatis, resp Arthritis deformans, Prag med Wchnschr **26** 493-494, 508-509, 521-523 and 531-533, 1901

occurred. Kast expressed the belief that there is a fundamental difference between those instances of acute onset (secondary chronic arthritis), in 75 per cent of which there was endocarditis, and those of insidious onset (primary chronic arthritis), in only 30.8 per cent of which endocarditis or pericarditis occurred.

Gzimek,¹⁷ in 1932, found that in 39 (42.8 per cent) out of 91 cases of "genuine arthritis deformans" (rheumatoid?) recurrent or healed valvular disease was present. He included in his study only cases in which exostoses (*Randwucherungen*) were present on joint margins. He excluded all cases of "genuine arthritis deformans" in which acute endocarditis was present. Because of this exclusion and the fact that the type of arthritis that he studied was not clearly defined, his results are difficult to interpret.

The relative lack of careful anatomic studies of the heart in cases of chronic infectious (rheumatoid) arthritis is in contrast to the large number of such studies in cases of rheumatic fever. Therefore, the present study was undertaken. We also hoped that such an investigation might throw light on the relationship between rheumatic fever and chronic infectious arthritis.

MATERIAL AND METHODS

This investigation was based on a study of the necropsies in 25 cases of chronic infectious (rheumatoid) arthritis, in only 2 of which there was a history of rheumatic fever. The pathologic material at the Mayo Clinic was surveyed, and all cases were included in which the following clinical criteria in regard to the joint disease had been fulfilled. All patients whose cases were included in this study had polyarticular inflammation, generally the onset had been insidious, although occasionally the beginning had been explosive. In each instance, the arthritis had run a progressive course for months or years. There was always some degree of articular crippling. In some, the joint disease had become relatively inactive but it had always caused changes which were easily detectable on clinical examination. Many of the involved joints had a spindle-shaped appearance because of swelling of the joint accompanied by atrophy of the adjacent muscles. Periarticular and synovial thickening were common, and frequently effusions were present. Some degree of fibrous ankylosis was a usual finding.

Roentgenograms were frequently normal in early stages, although in well developed stages there were swelling of periarticular soft parts, narrowing of the joint space, atrophy of epiphyseal bone, destruction of subchondral bone and, later, marginalipping.

Systemic manifestations were usually present, these frequently included slight fever and loss of weight associated with some degree of hypochromic anemia. The concentration of hemoglobin averaged 66.6 per cent in these cases. The number of erythrocytes per cubic millimeter of blood averaged approximately 3,990,000.

In each instance, the diagnosis of rheumatoid arthritis had been made by a consultant of the Section on Arthritis of the Mayo Clinic.

17 Grzimek, N. Ueber die Häufigkeit des Zusammentreffens von Arthritis deformans und chronischer Endokarditis, *Virchows Arch f path Anat* **286** 286-290, 1932.

TABLE 1—Clinical Data and Necropsy Observations on the Heart of Twenty-Three Cases of Chronic Infectious Arthritis

Case No and Sex	Age, Years		Clinical Findings in Joints	Report of Roentgenograms of Joints	Hemo globin, Red Blood Cells	Pathologic Diagnosis of Heart Lesion
	At Onset of Arthritis	At Death				
1 M	48	55	Shoulder movements limited, 3, flexion deformity of right elbow, 45 degrees, atrophy of interosseous muscles of hands, spindle shaped swellings of midphalangeal joints of fingers, flexion deformities of right knee, 30 degrees, and left knee, 60 degrees	Hypertrophic changes around knee joints	70% 4,240,000	Subacute rheumatic mitral and aortic valvulitis, coronary arteritis, acute (focal and diffuse) myocarditis
2 M	11	17	Swollen knees held in flexion deformity of 80 degrees spindle shaped swellings of midphalangeal joints of hands, atrophy of interosseous muscles of hands, shoulder movements limited, 2 ankylosis of wrists and elbows, swollen and rigid feet	Knees markedly swollen, bones osteoporotic	50% 3,590,000	Subacute rheumatic pericarditis with beginning organization, acute and chronic focal myocarditis
3 F	22	24	Duration of arthritis 25 months, spindle shaped swellings of midphalangeal joints of fingers, elbows, wrists, knees and ankles swollen and motion limited, flexion deformities of elbows and knees, extreme atrophy of muscles adjoining affected joints, characteristic of chronic infectious arthritis, spondylitis present	Evidence of atrophic arthritis of both hands	65% 4,210,000	Subacute rheumatic mitral endocarditis, fibrinous pericarditis, diffuse and nodular myocarditis, and coronary arteritis
4 M	42	48	Shoulder motions painful, flexion deformity of left elbow 5 degrees, and right elbow 10 degrees, left wrist swollen and tender, knuckles swollen and tender, hip motions limited, right 1 and left 1+, right knee swollen, 2, fluid present, left knee swollen, 1+, metatarsal joints tender	Narrowing of joint spaces, with swelling of soft tissues and osteoporosis of knees, left hand and right wrist and foot	3,710,000	Chronic active rheumatic mitral endocarditis with noninfected thrombus attached, acute and chronic rheumatic and focal aortitis
5 F	22	24	Jaw movements limited, 2, swelling of proximal, interphalangeal and metacarpophalangeal joints, elbows limited, 1, movements of both shoulders limited, knees and feet stiff	Periarticular swelling of joints of hands	92 7% 4,500,000	Chronic rheumatic adhesive pericarditis with subacute exacerbation
6 F	45	57	A wheel chair invalid because of pain, heat and swelling of many joints, flexion deformities of knees, spondylitis present	Marked destructive arthritis of knees and hands accompanied by ankylosis	70% 4,010,000	Active chronic rheumatic endocarditis of mitral, aortic and tricuspid valves, aortitis and pericarditis, acute pulmonary endocarditis, chronic diffuse and focal myocarditis (mitral stenosis, grade 2)
7 F	30	49	Deformities of joints of hands and feet characteristic of chronic infectious arthritis, subluxation and aduction of fingers			Acute exacerbation of chronic rheumatic obliterative pericarditis, acute focal myocarditis, acute coronary periarthritis, chronic healed (?) mitral endocarditis
8 F	12	14	Jaws and all large joints limited, knees and ankles almost completely ankylosed	Evidence of atrophic arthritis in wrists and fingers	46% 3,420,000	Chronic active rheumatic mitral endocarditis and myocarditis, chronic aortic and tricuspid endocarditis
9 F	38	42	Motion of jaws limited, left shoulder and wrists with limited motion, slight flexion deformities of elbows, spindle shaped swellings of midphalangeal joints, metatarsal joints tender			Chronic rheumatic mitral endocarditis and healed rheumatic myocarditis (mitral stenosis, grade 2+)
10	60	63	Rheumatoid arthritis with "horrible deformities" activity of inflammatory process only slight	Soft tissue swelling of knees with flexion deformities	53%	Chronic rheumatic mitral and aortic endocarditis with calcification, healed rheumatic myocarditis (aortic stenosis, grade 1)

11 M	52	52	Duration of arthritis 5 months, midphalangeal joints of right hand swollen, swollen tender metatarsal joints	Normal	97 3% 4,100,000	Inactive rheumatic mitral endocarditis with an organizing thrombus
12 F	46	49	Right ankle, midphalangeal joints and left wrist swollen and red	Swelling of soft tissues and destruction of cartilage of right ankle	93 3% 4,130,000	Inactive rheumatic mitral and aortic endocarditis with stenosis of mitral valve (mitral stenosis, grade 3)
13 F	30	53	Shoulder motions limited, flexion deformities of knees, right 15 degrees, left 20 degrees, right wrist limited, atrophy of interosseous muscles of hands with hyperextension deformities of midphalangeal joints of hands, limitation of motion in right hip	Destructive type of arthritis of right knee with marked periarticular swelling	70% 4,520,000	Inactive rheumatic mitral endocarditis (mitral stenosis, grade 3)
14 M	32	38	Limitation of motion of elbows, wrists and ankles, swollen midphalangeal joints of hands, flexion deformities of knees	Ankylosis of knees	25% 2,710,000	Inactive rheumatic mitral endocarditis, acute focal myocarditis (rheumatic?)
15 F	?	32	Flexion deformities of elbows and knees, limited motion of fingers, wrists, elbows, shoulders, knees and ankles, knees swollen and boggy, ulnar deviation of fingers, spondylitis	Hypertrophic changes in knee joints	60% 4,000,000	Thrombosis of right coronary artery, old infarct of myocardium
16 M	51	51	Hips limited, 1, right knee swollen	Destructive arthritis in knee joints	65% 4,150,000	Nonspecific pericarditis
17 M	35	37	Spindle shaped swellings of midphalangeal joints of hands, flexion deformities of elbows, pain on abduction of shoulders, painful feet	Hands normal	58% 4,700,000	Hypertrophy of heart, 140 Gm (hypertension)
18 M	21	34	Extensive spondylitis, thoracic expansion reduced	Destructive arthritis of both sacroiliac joints and 3d and 4th lumbar vertebrae	110%	Old infarct of myocardium
19 M	47	47	Swelling of proximal and midphalangeal joints of hands with atrophy of interosseous muscles and inability to close fists, right elbow, neck and shoulders limited, thoracic expansion, 1 inch (2.5 cm)	Periarticular swelling of joints of hands with osteoporosis due to atrophic arthritis	70% 4,100,000	Hydropéricardium (300 cc)
20 M	7	26	Flexion deformities of hips and knees ankylosis of shoulders, elbows and wrists	Destructive arthritis of right knee with ankylosis of right shoulder, elbow, wrist and hand		Obliterative fibrous pericarditis (rheumatic?)
21 M	55	55	Characteristic deformities of chronic infectious arthritis in joints of fingers, elbows and feet			Normal
22 F	39	69	Ankylosis of wrists and fingers, flexion deformities of knees, 15 degrees	Marked hypertrophic changes in both knees, with destruction of cartilage	93 3% 4,100,000	Normal
23 F	26	30	Multiple ankylosis and contractures, only 30 degrees of motion in left elbow, left wrist ankylosed, contractures of finger joints	Destruction of cartilage of knee joint and fixation of patella due to chronic infectious arthritis	70% 4,300,000	Normal
24 M	?	47	Lumbar and dorsal portion of spine fixed because of spondylitis	Normal		Normal
25 M	19	22	Spondylitis with 90 per cent fixation of spine, atrophy of interosseous muscles of hands, swollen wrists and metacarpophalangeal joints, spindle shaped swellings of midphalangeal joints, flexion deformities right elbow, 20 degrees, left, 30 degrees, only 20 degree motion in hips and knees	Synovial swelling in knees associated with some ankylosis	45% 3,230,000	Normal

After careful gross examination at the time of necropsy the hearts were fixed in modified Kaiserling's¹⁸ solution and then were preserved in neutral solution of formaldehyde U S P Sections for histologic study were taken of all structures that presented abnormal appearances In addition, routine sections were taken from the mitral and aortic valves and valve rings, from the anterior wall and apex of the left ventricle, as well as from the posterior base of the septum and from the posterior wall of the left auricle The sections were stained routinely with hematoxylin and eosin The Van Gieson, Weigert fibrin and Gram stains and the Pappenheim pyronine and de Galantha¹⁹ silver stains were employed when indicated

RESULTS

The results of this study have been summarized in table 1 There were 20 cases of chronic infectious arthritis with which cardiac damage was associated Lesions indistinguishable from those produced by rheumatic fever were found in 14, and nonrheumatic lesions were present in 5 In 1 case there was fibrous obliteration of the pericardial cavity, but the nature of this lesion could not be determined because neither the heart nor the histologic sections had been preserved A normal heart was found in only 5 instances

Lesions not attributable to rheumatic fever were as follows coronary sclerosis with thrombosis and acute and chronic infarction of the myocardium (case 15), nonspecific subacute fibrinous pericarditis (case 16), hypertrophy of the heart as a result of hypertension (case 17), coronary sclerosis with chronic infarction of the myocardium (case 18), hydropericardium (case 19) and obliteration of the pericardial sac (case 20)

GROSS APPEARANCE OF RHEUMATIC LESIONS

In all but 1 (case 1) of the 14 cases in which rheumatic lesions were demonstrated in the heart, the lesions had been diagnosed at the time of necropsy from the gross appearance

Gross lesions were present in the mitral valve in 10 cases In 5 (cases 3, 9, 11, 13 and 14) the mitral valve was the only one involved, in 3 (cases 4, 10 and 12) both the mitral and the aortic valve were involved, and in 2 (cases 6 and 8) the mitral, aortic and tricuspid valves were involved

The changes present consisted of variable degrees of diffuse thickening of the leaflets of the mitral valve with shortening and thickening of the chordae tendineae Verrucae were present in only 5 cases (3, 6, 8, 9 and 14), and in 2 instances uninfected thrombi were attached to the leaflet (cases 4 and 11) Gross evidence of calcification was present in only 1 instance (case 13) In several instances vascularization of the leaflet was grossly apparent

18 Robertson, H E, and Lundquist, R The Preparation of Pathologic Specimens for Exhibition Purposes, *J Tech Methods* **13** 31-32, 1934

19 de Galantha, E Personal communication to the authors

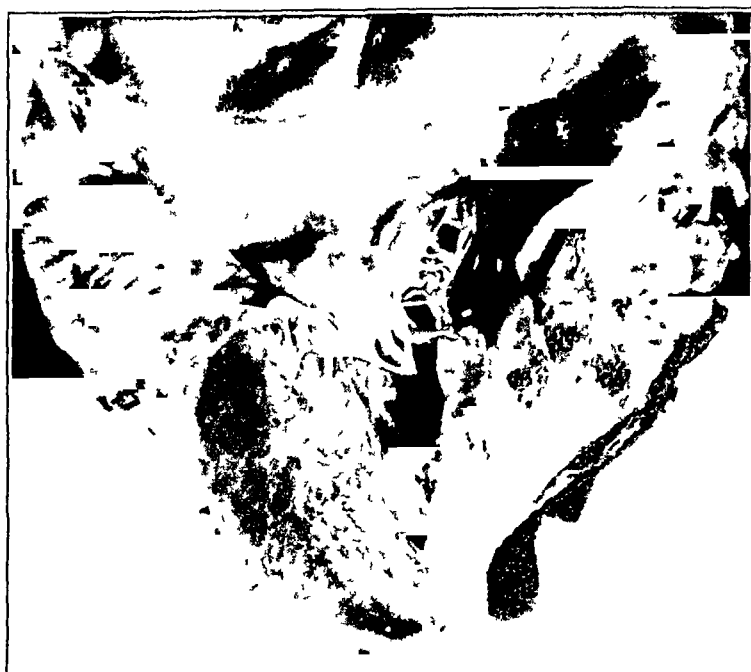


Fig 1 (case 13) —Thickening of the mitral leaflet with thickening and shortening of the chordae tendineae Dilatation of the left auricle

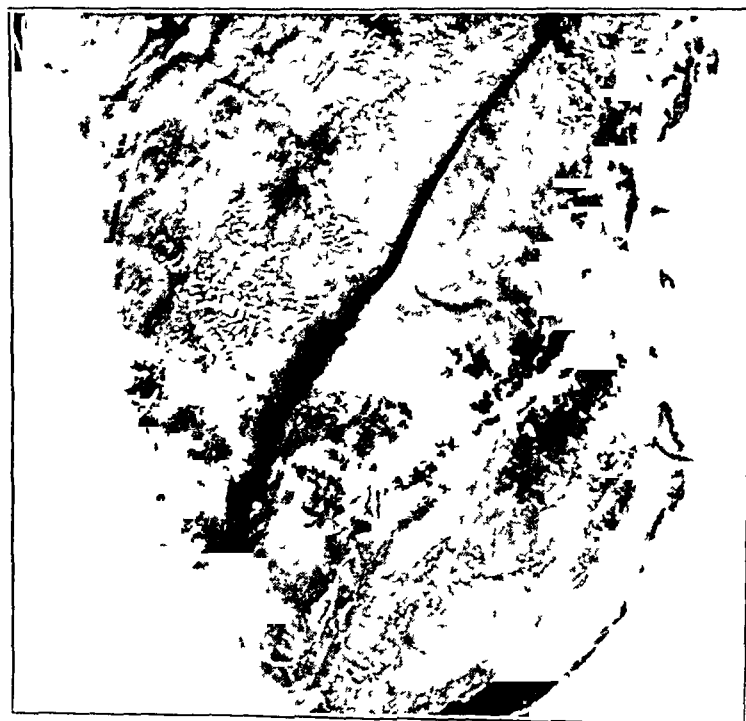


Fig 2 (case 2) —Subacute fibrinous pericarditis

These changes had resulted in severe stenosis of the mitral valve in cases 12 and 13 (fig 1) and moderate stenosis in 2 others (cases 6 and 9). The left auricle was dilated in these 4 cases, and in 1 instance (case 12) there was a mural thrombus in the left auricular appendage.

The aortic valve revealed gross evidence of injury in 5 cases. Thickening and stiffening of the leaflets occurred in 2 cases (6 and 8), adhesions between the cusps at the commissures were present in 2 (cases 4 and 10), and in 1 instance (case 6) there was rounding of the free edge with consequent shortening of the leaflet. Mild stenosis was present with nodular calcification of the leaflets in a single instance (case 10). The leaflets of the tricuspid valve were irregularly thickened in 2 cases (6 and 8). The pulmonary valve revealed no gross indication of valvulitis.

The pericardium was involved in 5 cases. In 3 of these (cases 2, 5 and 7) the pericardium was the only structure that revealed gross evidence of injury, whereas in 2 others (cases 3 and 6) pericarditis was accompanied by rheumatic valvulitis and aortitis. In 3 instances (cases 2, 3 and 5) the pericardial exudate was predominantly fibrinous (fig 2), in 1 instance (case 6) it was fibrinopurulent, and in another (case 7) there was obliteration of the pericardial sac by fibrous adhesions and calcified masses were present in the obliterated sac.

Chronic infarction was present in case 7 and perivascular scars occurred in case 14. These were the only cases in which there was macroscopic evidence of myocardial disease. Verrucae on the endocardium of the left auricle were present in only 1 instance (case 6).

The mean weight of the hearts in which rheumatic lesions were demonstrated was 379.7 Gm. The mean age of these patients was 42.3 years. The largest heart (case 6) weighed 547 Gm, and the smallest (case 4), 260 Gm. The weights varied between 300 and 400 Gm in 7 cases and were more than 400 Gm in 4 cases. The mean weight of the hearts in 5 cases in which nonrheumatic lesions were demonstrated was 386 Gm. The largest heart in this group weighed 620 Gm (case 16), and the smallest, 263 Gm (case 19). The mean weight of the hearts without lesions was 249.6 Gm, the largest weighed 280 Gm (case 21), and the smallest, 222 Gm (case 25). It is apparent that in the cases in which there are associated cardiac lesions the mean weight of the heart is higher than is generally accepted as normal and in those in which there are no associated cardiac lesions the mean weight is slightly less than normal.

HISTOLOGIC FEATURES OF RHEUMATIC LESIONS

For convenience of description and discussion, the cases studied may be separated into groups distinguished by the presence of (1) subacute, (2) chronic and (3) inactive lesions. There were 3 instances of subacute, 7 instances of chronic active and 4 instances of inactive rheumatic

lesions in the heart This does not mean, however, that all the lesions in a single group of cases were of the same type It simply means that the predominant type of inflammation in any single case could histologically be classified as subacute, chronic or inactive In group 2, for example, there were many instances, as will be emphasized subsequently, in which evidence of acute or subacute inflammation was found in addition to the chronic inflammation In table 2, the lesions have also been classified as to their respective sites

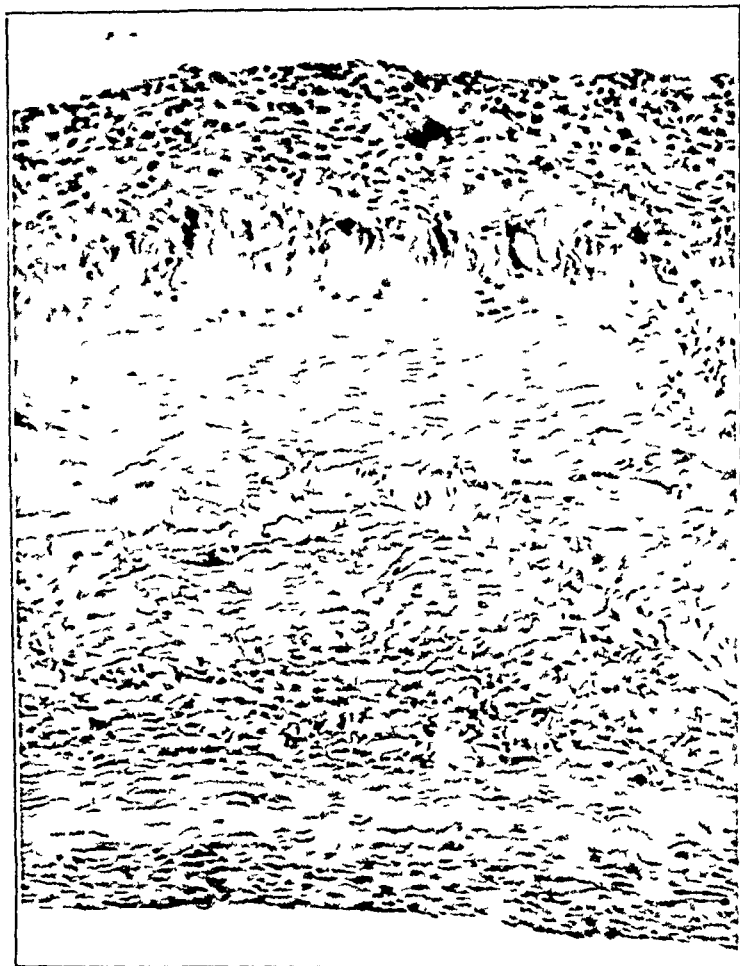


Fig 3 (case 1)—Subacute aortic rheumatic valvulitis Palisading of the basophilic cells around a region of fibrinoid degeneration Hematoxylin and eosin, $\times 200$

TABLE 2—*Sites of Rheumatic Lesions*

Structures Involved	Number of Cases
Mitral valve only	6
Mitral and aortic valves	3
Mitral, aortic and tricuspid valves	1
Mitral, aortic, tricuspid and pulmonary valves	1
Pericardium	5
Myocardium	12
Left auricle	3
Root of aorta	3
Coronary arteries	3

Subacute Lesions—In this group are cases 1, 2 and 3. The valves involved were the mitral and the aortic in case 1 and only the mitral in case 3. In each instance there was severe valvulitis of the entire leaflet with involvement of the valve rings as well. The lesions were typical of those seen in valves in cases of rheumatic fever. Regions of fibrinoid degeneration with large basophilic histiocytes showing a tendency toward a palisaded arrangement were present (fig 3).

Diffuse fibrinous pericarditis occurred in 2 instances (cases 2 and 3). Myocarditis was present in all 3 cases of this group. The inflammation of the heart muscle was both diffuse and nodular. In cases 2 and 3 evidence of chronic as well as acute and subacute myocarditis was present. In both of these cases, polymorphonuclear cells were numerous in many of the myocardial lesions and in some regions there were small abscesses. Typical Aschoff bodies were present in all of these cases.

Coronary arteries were involved in cases 1 and 3. In the former the entire wall of the right coronary artery was the seat of subacute inflammation, whereas in the latter only the smaller branches were involved, apparently by extension from the perivascular lesions.

It is interesting to note that in case 1 macroscopic examination of the heart had revealed no lesions, whereas extensive damage was found on microscopic examination.

Chronic and Active Lesions—In this group of 7 cases, there were 2 (cases 4 and 9) in which only the mitral valve was involved, 1 (case 10) in which both the mitral and the aortic valve were involved, 1 (case 8) in which the mitral, aortic and tricuspid valves were involved and 1 (case 6) in which all the valves were involved.

The most pronounced valvular changes in this group consisted of thickening and vascularization of the mitral leaflets. The thickening was due to an increase of hyalinized collagenous connective tissue generally present throughout the valve, but found especially in the auricularis layer of the auriculoventricular valves. The spongiosa was also frequently replaced by this dense hyalinized connective tissue. Vascularization occurred in the mitral valve in 3 cases (cases 7, 8 and 9), the vessels being thick-walled arteries. In addition to these evidences of a former inflammatory process, there were foci of histiocytic and fibroblastic proliferation in various portions of the leaflet (fig 4a). In 3 cases of this group (cases 6, 8 and 9) there were Aschoff bodies in the mitral valve. Small, irregular fibrous nodules were present on the surface of the mitral leaflets in 4 cases (cases 6, 7, 8 and 9). These probably represented organized verrucae.

Lesions were noted in the ring of the mitral valve in 4 cases of this group. Abnormal vascularization was present in 3 (cases 6, 9 and 10), and in 1 (case 6) there were collections of inflammatory cells also. Fibrous polypoid projections from the subvalvular angle of the mitral leaflet occurred in 2 instances (cases 6 and 9).

The aortic valve was less frequently involved, but the histologic changes were similar to those seen in the mitral valve. Thickening of the leaflets was prominent especially in the ventricularis layer. Aschoff bodies occurred in the leaflet in only 1 instance (case 6). Abnormal vascularization in the aortic ring was present in 2 instances (cases 4 and 10), and inflammation was present in 1 (case 6).

In this group in which chronic active lesions were present, the pericardium was involved in 3 instances (cases 5, 6 and 7). In addition to fibrous adhesions between the parietal and the visceral layer, there were regions of fibinous exudate with polymorphonuclear cells and collections of proliferating histiocytes. The latter were large and contained baso-

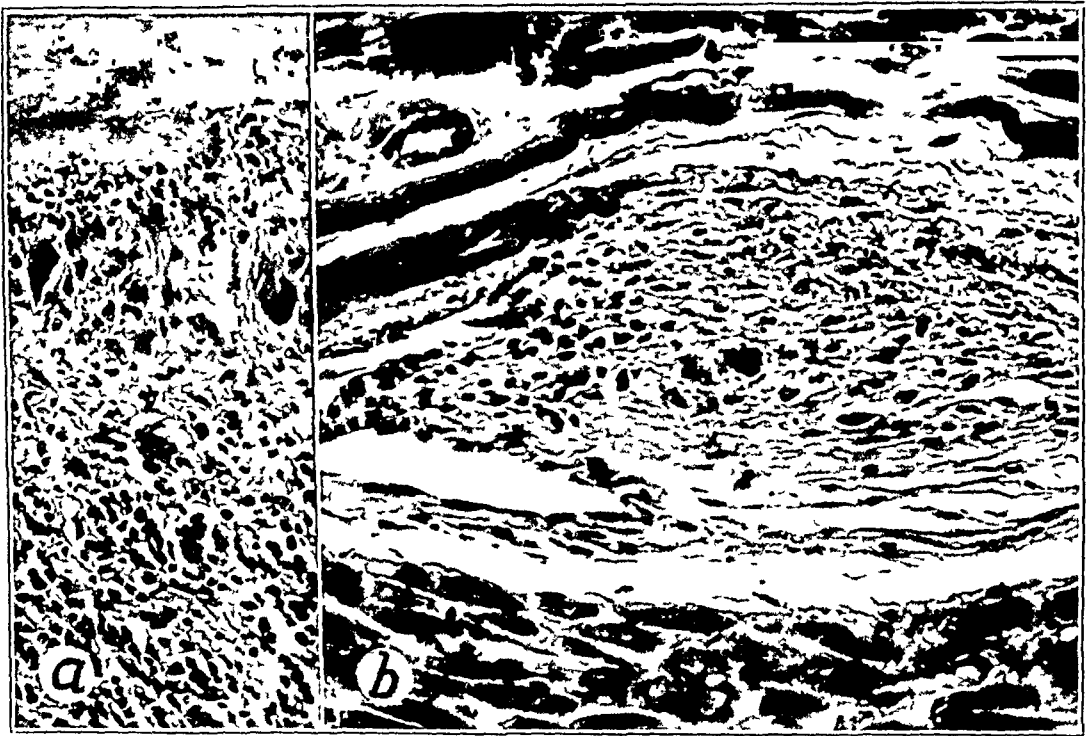


Fig 4—Chronic rheumatic lesions. (a) Rheumatic mitral valvulitis (case 6). Large basophilic and giant cells are arranged about a region of necrosis. Hematoxylin and eosin, $\times 195$. (b) Myocardial Aschoff body (case 8). Hematoxylin and eosin, $\times 245$.

philic cytoplasm and large pale nuclei. Occasionally giant cells were noted. The cells had a tendency to be arranged in palisades.

Lesions were present in the myocardium in each case of this group. In 2 instances (cases 9 and 10) the only evidence of myocardial injury was the presence of perivascular "onion skin" scars. In 2 cases the myocardium appeared to be involved by extension, in 1 (case 4) from an aortic lesion and in the other (case 5) from a pericardial lesion. In 3 other instances (cases 6, 7 and 8) typical Aschoff bodies were present (fig 4 b), while in 1 instance (case 6) there was also diffuse myocarditis.

The left auricle was the site of injury in 3 cases of this group in which chronic active lesions were present. In 1 (case 6) there were mural endocardial verrucae as well as auricular myocarditis, in 1 (case 7) there was auricular myocarditis only, and in 1 (case 4) there was thickening of the endocardium due to fibrous and elastic tissue.

Nonspecific lesions in the coronary arteries were present in 3 cases of this second group (cases 5, 6 and 10) and consisted of organized mural thrombi in the smaller branches. In 1 case (case 10) this lesion was associated with chronic infarction of the myocardium. Rheumatic periarteritis occurred in case 7. The aorta was the site of granulomatous lesions in 2 cases (cases 4 and 6), and typical Aschoff bodies were

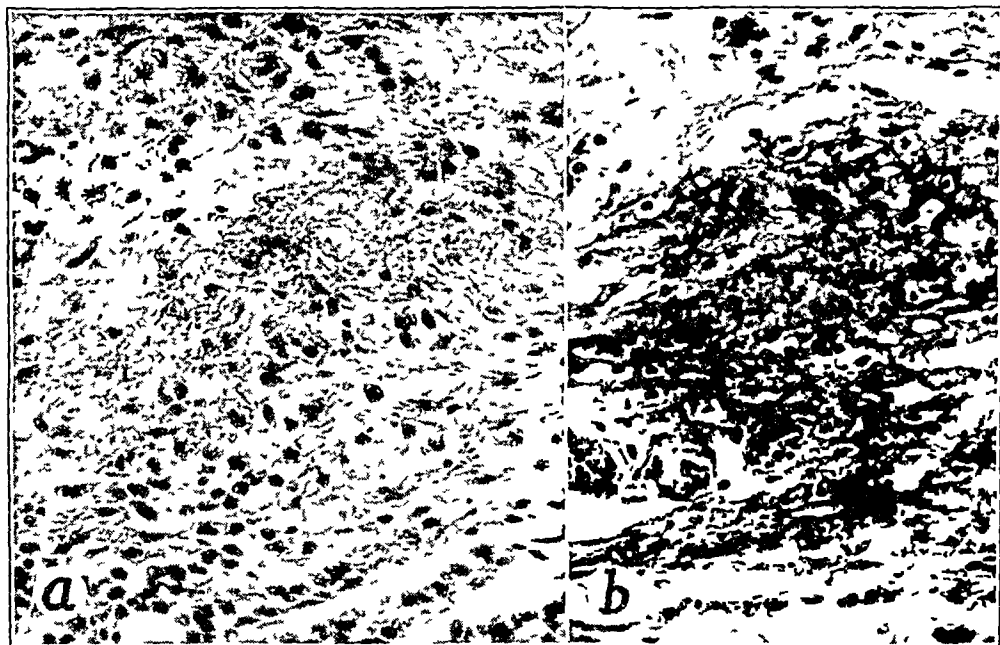


Fig 5—Fibrinoid degeneration in cases with associated chronic rheumatic lesions. (a) Region of fibrinoid degeneration and proliferation of histiocytes in adventitia of aorta (case 4). Hematoxylin and eosin, $\times 205$. (b) Region of acute fibrinoid degeneration in otherwise chronic pericarditis (case 7). Hematoxylin and eosin, $\times 225$.

present in both. Deposits of calcium, either in the mitral or in the aortic valve or in the pericardium, occurred in 4 cases of this group (cases 6, 7, 9 and 10). It is significant that typical Aschoff bodies, in the valves, the pericardium or the myocardium, were found in all of the cases of this group in which chronic active lesions were present, except in cases 9 and 10.

A significant feature of the cases of this group also was the fact that in 5 of them evidence of recent acute rheumatic injury was found in addition to the chronic inflammation. The acute lesions were in some instances superimposed on inactive or chronic inflammatory processes,

and in other instances they appeared in a previously uninvolved region of the heart. Thus, in case 4 chronic mitral endocarditis was associated with regions of "fibrinoid" degeneration and proliferative inflammation in the aorta and myocardium (fig 5). In case 5 the pericardial sac was obliterated by fibrous adhesions, yet lesions with fibrinous exudate and proliferating histiocytes in both epicardium and myocardium were also found. In case 6 chronic but extremely active lesions in the mitral and the aortic valves, the pericardium and the aorta were accompanied by acute endocarditis of the pulmonary valve. In case 7 there was an acute recurrence of chronic adhesive pericarditis in addition to acute lesions of the myocardium and the coronary arteries (fig 5). In case 8

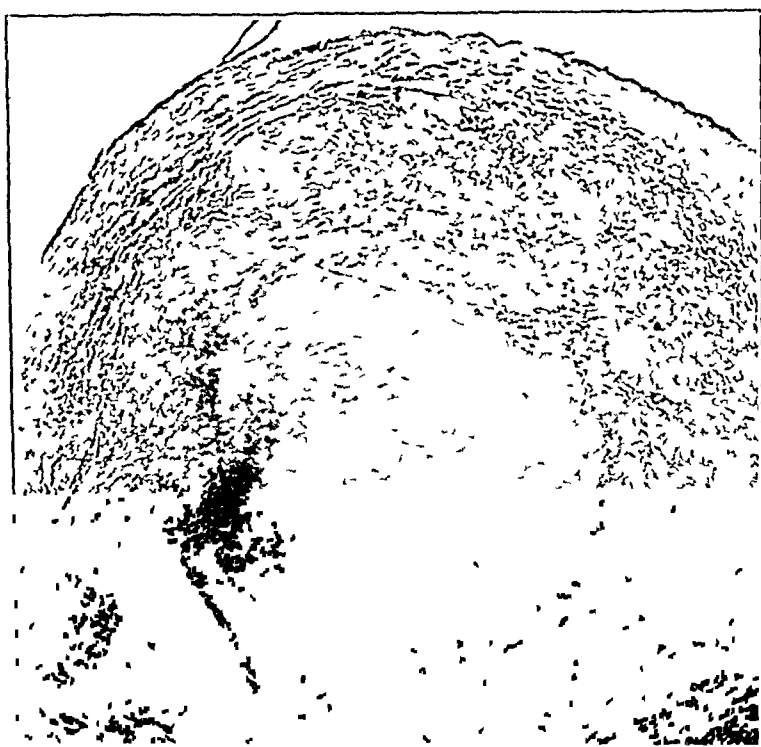


Fig 6 (case 6) —Chronic "rheumatic" inflammation of the aortic valve with a large central region of necrosis surrounded by proliferating histiocytes and fibroblasts. Hematoxylin and eosin, $\times 32$.

a region of acute "fibrinoid" degeneration occurred in the spongiosa of the mitral valve. This valve had been already thickened by chronic proliferative inflammation.

One case (case 6) in this second group deserves special mention in that the lesions were in many respects similar to those seen in the subcutaneous nodules of chronic infectious (rheumatoid) arthritis. In the pericardium, in the mitral and the aortic valves and in the aorta there were massive proliferations of large histiocytes containing basophilic cytoplasm arranged radially around large central regions of necrosis (fig 6). Many giant cells were present, and more or less typical Aschoff

bodies could also be seen. The myocardium was the seat of diffuse interstitial myocarditis, but an occasional Aschoff body could also be found. Search was made for *Spinochaeta pallida* and for tubercle bacilli in specially stained sections, but none were found.

Inactive Lesions—In this group were 4 cases (cases 11, 12, 13 and 14) in which the macroscopic lesions were found on histologic examination to be burned out or inactive. The mitral valve was involved in all of these, and in 1 instance (case 12) the aortic valve was also injured. The valvular lesions consisted of changes similar to those described for the second group except that no evidence of activity such as regions of fibrinoid degeneration or granulomatous foci could be found. Vascularization of the valve, with thick-walled vessels, was present in 3 instances (cases 12, 13 and 14). Vascularization of the valve rings occurred in 2 instances (cases 11 and 12). Deposits of calcium were found in the mitral valve in 2 instances (cases 11 and 13) in this group.

The ventricular myocardium and septum revealed lesions in 2 cases. In 1 (case 12) the only sign of myocardial damage was the presence of perivascular "onion skin" scars, whereas in the other (case 14) there were scattered foci of interstitial proliferative inflammation but typical Aschoff bodies were not present. Examination of the pericardium, the left auricle and the coronary arteries revealed no lesions in the cases of this group.

CLINICAL CONSIDERATIONS

The cases of 14 male and 11 female patients were included in this study. The mean age was 41 years. Clinically, the joint disease showed some evidences of activity in all cases. Some workers would distinguish between chronic infectious arthritis with an acute onset and chronic infectious arthritis with an insidious onset. Pirram, Kast and Kahlmeter, as noted previously, have found a higher incidence of cardiac damage in those cases in which an acute onset occurred. In all but 3 of our series (cases 3, 16 and 20) the onset of the disease was insidious. Subacute rheumatic lesions were found in the pericardium, the mitral valve and the myocardium in case 3, nonspecific subacute pericarditis was present in case 16 and obliteration of the pericardial sac occurred in case 20. The specimen in the last case, unfortunately, had not been saved, and consequently its rheumatic or nonrheumatic nature could not be determined.

It is of interest to examine our material in the light of Garrod's contention that the occurrence of cardiac lesions among patients who have chronic arthritis can be attributed to a previous attack of rheumatic fever. In the present series, a history of rheumatic fever could be elicited in only 2 instances (cases 5 and 9). Rheumatic lesions in the heart were present in both. In 1 there was pericarditis and in the other mitral

endocarditis and myocarditis. The possibility that all the other patients also had previous independent attacks of rheumatic fever cannot, of course, be excluded, but this hardly appears likely. In all the material available for necropsy at the Mayo Clinic, the incidence of cardiac lesions of rheumatic fever is 5 per cent.

Comparison of the clinical data regarding the cardiac status of our patients with lesions subsequently demonstrated at necropsy reveals that in only 7 of the 14 cases in which rheumatic lesions occurred was there any clinical evidence of heart disease. In 6 of these (cases 3, 8, 9, 10, 12 and 13) the mitral valve was affected, and in 2 (cases 9 and 12) there was severe mitral stenosis. In 5 of the cases (cases 2, 3, 8, 9 and 10) lesions in the myocardium occurred. Subacute rheumatic pericarditis occurred in 2 (cases 2 and 3). Of the remaining 7 cases in which rheumatic heart lesions were present at necropsy, the patients in 6 were known to have had no clinical signs or symptoms of heart disease, and in 1 case there had been no clinical examination for six years before death, which occurred suddenly at the patient's home (case 6).

Of the 6 cases in which nonrheumatic lesions were observed at necropsy, signs and symptoms of heart disease were present clinically in only 2. In 1 (case 17) there was hypertrophy of the heart resulting from hypertension, and in the other (case 15) coronary thrombosis with acute and chronic infarction of the myocardium had occurred.

The causes of death in these cases of chronic infectious arthritis were varied. Cardiac disease was considered a primary or important contributory cause of death in 7 of the 14 cases in which rheumatic heart lesions were found at necropsy (cases 1, 2, 3, 6, 8, 9 and 12).

In the group of 6 cases in which nonrheumatic heart lesions were observed at necropsy, the cardiac injury was considered a contributory cause of death in 2 instances.

COMMENT

Many pathologists are of the opinion that the lesions of rheumatic fever can be diagnosed with the same degree of accuracy as can lesions of tuberculosis and syphilis. There is, however, considerable controversy regarding the specificity of the Aschoff nodule in the diagnosis of rheumatic heart disease. Fahr,²⁰ Rhoads,²¹ Clawson²² and others have observed similar lesions in such varying conditions as scarlet fever, meningococcic endocarditis and subacute bacterial endocarditis. Some

20 Fahr, T. Beiträge zur Frage der Herz- und Gelenkveränderungen bei Gelenkrheumatismus und Scharlach, *Virchows Arch f path Anat* **232** 134-159, 1921.

21 Rhoads, C. P. Vegetative Endocarditis Due to the Meningococcus, with a Case Report, *Am J Path* **3** 623-630 (Nov) 1927.

22 Clawson, B. J. The Aschoff Nodule, *Arch Path* **8** 664-685 (Oct) 1929.

workers, notably Fahr²³ and Aschoff,²⁴ have denied the histologic identity of these lesions. There can be little doubt, however, that in the absence of the aforementioned diseases the typical Aschoff body should be held as evidence for rheumatic heart disease. There can also be no denial of the fact that rheumatic heart disease can often be diagnosed accurately in the absence of typical Aschoff bodies if other characteristic changes are present.

The rheumatic nature of the subacute and chronic lesions described in the first 10 cases of our series cannot be seriously disputed. Aschoff bodies in various stages of development were found in the myocardium, valves or pericardium in all but 2 cases. In these 2 (cases 9 and 10) the character of the valvular changes (thickening of the mitral leaflets, thickening and shortening of the chordae tendineae and mitral stenosis) was sufficiently characteristic to make possible an unequivocal diagnosis of rheumatic heart disease. Histologically, the diagnosis was supported by the finding of proliferation of histiocytes and fibroblasts in the valves, together with numerous perivascular scars in the myocardium.

In the 4 cases of group 3 in which histologically inactive lesions were present, our diagnosis may perhaps be questioned. The macroscopic appearance of these lesions, however, was typical of rheumatic heart disease. Thus, severe mitral stenosis occurred in 2 cases (cases 12 and 13), whereas in the other 2 there were milder, but none the less typical, changes of healed rheumatic endocarditis (thickening of mitral leaflets and chordae tendineae and in 1 instance organized verrucae on the mitral leaflet).

The histologic appearance of these lesions was characteristic of old, "burned-out" rheumatic lesions. The possibility that these changes might have been produced by some infection other than that responsible for rheumatic fever cannot of course be entirely excluded. It should be emphasized, however, that the cardiac lesions which occurred in this group differed in no way from lesions which have been repeatedly demonstrated in known cases of rheumatic fever.

Inasmuch as the argument might be advanced that some infection other than that responsible for rheumatic fever or chronic infectious arthritis was responsible for the occurrence or reactivation of the rheumatic cardiac lesions, it is interesting to note that evidence of acute terminal infection was present at necropsy in only 4 cases (bronchopneumonia in cases 4, 5 and 9 and streptococcal septicemia in case 13). Evidence of chronic infections was found in only 2 cases (pulmonary

23 Fahr, T. Vergleichende Herzuntersuchungen bei Scharlach, Streptokokkeninfektion und rheumatischer Granulomatose, Beitr. z. path. Anat. u. z. allg. Path. **85** 445-468 (Nov.) 1930.

24 Aschoff, L. Rheumatic Nodules in the Heart, Ann. Rheumat. Dis. **1** 161-166 (July) 1939.

tuberculosis in case 7 and chronic bronchiectasis in case 14) It is extremely unlikely that either infection was responsible for the cardiac lesions in these cases Their possible role in the reactivation of the lesions is unknown

We believe it is significant that in only 7 of our 14 cases in which rheumatic heart lesions were found did the patients have during life any ascertainable signs or symptoms of heart disease This would suggest that many patients with chronic infectious arthritis may have rheumatic cardiac lesions which are not severe enough to attract the attention of either the patient or the physician It indicates, furthermore, that one must draw a distinction between lesions which are actually present and those which are clinically apparent This study indicates that only by careful anatomic studies can the true incidence of cardiac lesions be determined in cases of chronic infectious arthritis

Several explanations for the comparative mildness of cardiac damage among patients with chronic infectious arthritis might be advanced The lack of severity might be attributed to the fact that the onset of chronic infectious arthritis is, as a general rule, later than the onset of rheumatic fever Thus, Dawson²⁵ stated that in 90 per cent of 257 patients with rheumatic fever the onset occurred before the age of 15 years, whereas in 90 per cent of 202 patients with chronic infectious arthritis the onset was after the age of 15 years The average age at onset in 23 cases of the present series in which this information was available was 33.9 years It is generally believed that the heart is more vulnerable to rheumatic infection in younger persons than in older ones

Hench²⁶ has suggested that the cardiac lesions associated with chronic infectious arthritis may go unrecognized by both the patient and the physician because patients with this disease are likely to lead a relatively restricted life in which an abnormally small tolerance of exercise is not noted The lesions might thus have greater opportunity to heal and less tendency to progress than they would among patients who have cardiac lesions and who after recovering from the articular manifestations of rheumatic fever subsequently resume full activity

Our anatomic observations, in general, support the clinical observations that the cardiac lesions associated with chronic infectious arthritis are not as severe or as widespread as such lesions are in the hearts of young persons who have rheumatic fever Nevertheless, the differences are of degree and not of kind Cardiac hypertrophy (weight of the heart more than 300 Gm) occurred in 11 of the cases in which there were rheumatic lesions, and in 7 cases of this group the cardiac injury played an important role in causing death

25 Dawson, M. H. Chronic Arthritis, in Nelson's New Loose-Leaf Medicine, New York, Thomas Nelson & Sons, 1937, vol. 5, pp. 605-644

26 Hench, P. S. The Systemic Nature of Chronic Infectious Arthritis, *Atlantic M. J.* 28: 425-436, 1925

It should also be emphasized that in all but 4 of the 14 cases there was histologic evidence of activity in the rheumatic lesions. This indicates that if a rheumatic lesion is clinically apparent, the chances are great that the process is still active. The importance of this fact should be considered in the decision regarding a patient's ability to pursue normal life and work.

The discovery in 14 of the 25 unselected cases of chronic infectious arthritis of cardiac lesions grossly and histologically similar to those associated with rheumatic fever suggests a definite relationship between these two diseases. Further evidence of this close relationship has been presented by Poynton,²⁷ Coates and Coombs,²⁸ Clawson and Wetherby,²⁹ Dawson³⁰ and Hawthorne³¹ on the basis of the histologic similarity of the subcutaneous nodules of the two diseases and by Klinge³² and his co-workers on the basis of certain anatomic similarities in the articular and the periarticular lesions, as well as in those in the heart.

The nature of this relationship is not clear and probably will not be understood until after the discovery of the etiologic agent or agents of these diseases.

SUMMARY AND CONCLUSIONS

In a study at necropsy of 25 cases of chronic infectious (rheumatoid) arthritis, cardiac lesions were demonstrated in 20. Lesions identical with those of rheumatic fever were observed in 14 (56 per cent). Non-rheumatic cardiac lesions were present in 6 (24 per cent). In 10 of the 14 cases in which there were rheumatic lesions there was histologic evidence that the inflammatory process was still active and progressive at the time death occurred. In 7 of the 14 instances associated with rheumatic cardiac lesions, the heart disease was judged to be an important factor in causing death. In only 7 of the 14 instances associated with rheumatic cardiac lesions had signs or symptoms of heart disease been present during life. The high incidence of rheumatic cardiac lesions in this series is suggestive of a relationship between chronic infectious (rheumatoid) arthritis and rheumatic fever.

27 Poynton, cited by Hawthorne³¹

28 Coates, V, and Coombs, C F. Observations on the Rheumatic Nodule, *Arch Dis Childhood* **1** 183-193, 1926

29 Clawson, B J, and Wetherby, M. Subcutaneous Nodules in Chronic Arthritis. Clinical, Pathological and Bacteriological Studies, *Am J Path* **8** 283-293 (May) 1932

30 Dawson, M H. A Comparative Study of Subcutaneous Nodules in Rheumatic Fever and Rheumatoid Arthritis, *J Exper Med* **57** 845-858 (May) 1933

31 Hawthorne, C O. On Subcutaneous Nodules, *Brit J Rheumat* **1** 109-117, 1938

32 Klinge, F. Der Rheumatismus, pathologisch-anatomische und experimentell-pathologische Tatsachen und ihre Auswertung für das ärztliche Rheumaproblem, *Ergebn d allg Path u path Anat* **27** 1-351, 1933

FAMILIAL NONHEMOLYTIC JAUNDICE
CONSTITUTIONAL HEPATIC DYSFUNCTION WITH INDIRECT
VAN DEN BERGH REACTION

WILLIAM DAMESHEK, M D
AND
KARL SINGER, M D
BOSTON

Jaundice of the familial type is almost invariably considered to be hemolytic. Congenital or familial hemolytic (acholuric) icterus is a well defined disease entity. That there are instances of familial icterus in which all the evidences of excessive blood destruction are lacking has only occasionally been recognized. We have recently observed two families in which, although bilirubinemia of the "indirect" type was present, there were the signs neither of hepatic disease nor of splenomegaly, increased fragility of the red cells or reticulocytosis. The urine was free of bilirubin and did not contain increased quantities of urobilinogen, and the results of hematologic examinations were uniformly normal. Final proof of the nonhemolytic character of the icterus in these families was obtained from study of the urobilinogen content of the feces, which was either normal or slightly decreased.

From 1900 to 1907, Gilbert and his associates¹ described a series of cases of congenital or familial icterus, which they divided into three main categories: (1) physiologic cholemia (normal), (2) simple familial cholemia, and (3) simple chronic icterus. The publications of Gilbert and his collaborators have been widely cited, and the few authors who discussed the possibility of a nonhemolytic, acholuric icterus usually referred to it as "Gilbert's disease." Careful perusal of the articles by Gilbert and his associates reveals that their cases of "familial cholemia" were in all probability examples of mild hemolytic jaundice. Later, after

From the Joseph H. Pratt Diagnostic Hospital and the Blood Clinic of the Boston Dispensary.

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1. Gilbert, A., Lereboullet, P., and Herschen, M. *Les trois cholémies congénitales*, Bull. et mém. Soc. méd. d'hôp. de Paris **24**: 1203, 1907. Gilbert, A., Castaigne, J., and Lereboullet, P. *De l'ictère familial*, *ibid.* **17**: 948, 1900.

Chauffard's extensive studies² of congenital hemolytic jaundice, the writings of Gilbert received diminishing attention, although his name persisted as a tag which served to identify a vague type of icterus without demonstrable pathologic change and without hemolytic character. Various authors have commented briefly on a condition which van den Bergh³ called "physiologic hyperbilirubinemia" and which was not infrequently noted in young people. Meulengracht⁴ has recently described the condition in a group of cases of mild jaundice as "icterus intermittens juvenilis." Rozendaal, Comfort and Snell,⁵ in their analysis of cases of slight and latent jaundice, referred briefly to a few cases of familial nonhemolytic, nonobstructive jaundice as possible examples of "constitutional hepatic dysfunction." Tecon⁶ differentiated two types of "hereditary hyperbilirubinemia," "familial cholemia" and hemolytic icterus.

It is the purpose of this paper to present observations made on two families with chronic, usually mild, nonhemolytic, nonobstructive, acholuric retention icterus. Although superficially the disease in these families resembled mild or latent hemolytic icterus, differentiation was readily made by laboratory studies. Results of the bilirubin excretion test indicated that disturbed permeability of the hepatic cells for bilirubin (retention jaundice) was probably present. Recognition of such a condition is important so that familial hemolytic jaundice may be ruled out.

METHODS

Hemoglobin—The Evelyn photoelectric method⁷ was used. One hundred per cent equals 15.6 Gm per hundred cubic centimeters of blood.

Red Cell Count, White Cell Count—Pipets and hemocytometers certified by the United States Bureau of Standards and an automatic shaker were used.

Platelet Count—The method of Dameshek⁸ was employed. The normal count is 400,000 to 900,000 per cubic millimeter.

2 Chauffard, M. A. Pathogenie de l'ictère congenital de l'adulte, *Semaine méd* **27** 25, 1907, Les ictères hémolytiques, *ibid* **28** 49, 1908.

3 Hijmans van den Bergh, A. A. Die Gallenfarbstoffe im Blute, Leiden, S. C. van Doesburgh, 1918.

4 Meulengracht, E. Icterus intermittens juvenilis (Chronischer intermittierender juveniler Subikterus), *Klin Wchnschr* **18** 118, 1939.

5 Rozendaal, H. M., Comfort, M. W., and Snell, A. M. Slight and Latent Jaundice, *J. A. M. A.* **104** 374 (Feb 2) 1935.

6 Tecon, R. M. A propos d'ictères chroniques, *Helvet med acta* **5** 671 1938, Les hyperbilirubinemies héréditaires. La cholemie familiale et l'ictère hémolytique, *Arch d mal de l'app digest* **28** 567, 1938.

7 Evelyn, K. A. Stabilized Photoelectric Colorimeter with Light Filters, *J Biol Chem* **115** 63, 1936.

8 Dameshek, W. A Method for the Simultaneous Enumeration of Blood Platelets and Reticulocytes, *Arch Int Med* **50** 579 (Oct) 1932.

Reticulocyte Count—The "dry" method, and films stained with brilliant cresyl blue and Wright's stain were used. The normal count is 0.0 to 1.0 per cent.

Hematocrit Reading—Venous blood was collected in 5 cc. vials containing 6 mg of dry ammonium oxalate and 4 mg of potassium oxalate⁹ and was centrifuged in Wintrobe hematocrit tubes for twenty-five minutes at 3,500 revolutions per minute.

Mean Corpuscular Volume—This is determined by the formula

$$\frac{\text{hematocrit reading} \times 10}{\text{red blood cells, in millions}}$$

The normal range is 84 to 94 (100) cubic microns.

Mean Corpuscular Diameter—Price-Jones curves were obtained by measuring the diameters of 200 cells directly, using a calibrated micrometer eyepiece. The average cell diameter normally is 7.4 to 7.6 microns.

Mean Corpuscular Thickness—The indirect method used is based on the formula

$$\frac{\text{mean corpuscular volume}}{\pi \left(\frac{D}{2}\right)^2}$$

in which D equals the mean corpuscular diameter. The normal thickness is approximately 1.9 to 2.4 microns. The direct method used was the method of Dameshek (unpublished). The thickness of red cells is measured directly from rouleaux with a micrometer eyepiece, 200 cells are measured. The normal range is 1.9 to 2.2 microns.

Spherocytic Index—The method of Heilmeyer,¹⁰ which is based on the formula $\frac{\text{mean cell thickness}}{\text{mean cell diameter}}$, was used. The normal figure is approximately 0.25, the normal range is 0.25 to 0.33.

Biopsy of Bone Marrow—The trephine method (Dameshek)¹¹ and the puncture method were used.

Fragility of Red Blood Cells to Hypotonic Solutions of Sodium Chloride—We employed the method of Daland and Worthley,¹² in which the red cells are adjusted to constant volume after being washed three times with physiologic solution of sodium chloride.

Fragility of Red Blood Cells to Lysolecithin—The method used was that of Singer,¹³ in which lysolecithin is obtained from normal serum and tested against

9 Heller, V. G., and Paul, H. Changes in Cell Volume Produced by Varying Concentrations of Different Anticoagulants, *J. Lab. & Clin. Med.* **19**: 777, 1934.

10 Heilmeyer, L. Die Sphärocytose als Ausdruck einer pathologischen Funktion der Milz, *Deutsches Arch. f. klin. Med.* **179**: 292, 1936.

11 Dameshek, W. Biopsy of the Sternal Bone-Marrow, *Am. J. M. Sc.* **190**: 617, 1935. Dameshek, W., Henstell, H. H., and Valentine, E. H. The Comparative Value and Limitations of the Trephine and Puncture Methods for Biopsy of the Sternal Bone-Marrow, *Ann. Int. Med.* **11**: 801, 1937.

12 Daland, G., and Worthley, K. The Resistance of Red Blood Cells to Hemolysis in Hypotonic Solutions of Sodium Chloride, *J. Lab. & Clin. Med.* **20**: 1122, 1934.

13 Singer, K. Das Problem der normalen und pathologischen Milzhamolyse, abstracted, *Wien. Arch. f. inn. Med.* **31**: 161, 1937. The Lysolecithin Fragility Test, *Am. J. M. Sc.* **199**: 466, 1940.

a constant volume of erythrocytes in geometrically increasing dilutions. A normal control and the red cells tested should give the same results. Thus far, abnormal, increased fragility has been found only in the congenital type of hemolytic icterus.

Icterus Index—The method of Meulengracht was used. The normal range is 6 to 8, 10 equals the high limit of the normal range.

Qualitative Measurement of Bilirubin—We employed the method of van den Bergh, "direct" and "indirect" reactions were noted.

Quantitative Measurement of Bilirubin—We employed the method of Malloy and Evelyn,¹⁴ using an Evelyn photoelectric colorimeter.

Urobilinogen in the Urine—The method of Wallace and Diamond,¹⁵ a roughly quantitative method applicable to specimens of freshly voided urine, was used. Normally a positive reaction occurs in dilutions of 1:10 and 1:20 occasionally in a dilution of 1:40.

Urobilinogen in the Feces—Quantitative determination was made by the method of Watson,¹⁶ which is based on the original method of Terwen^{16a} and the modification of Furth and Singer.¹⁷ The normal level of urobilinogen excretion is 40 to 150 mg. per day.

Galactose Tolerance Test—The method of Bauer¹⁸ was used. The excretion of more than 3 Gm. signifies hepatic damage.

Bromsulphalein Test—By the method of Rosenthal and White,¹⁹ an injection of 5 mg. per kilogram is given. Normally, less than 15 per cent should be present in the serum after half an hour.

Bilirubin Excretion Test—By the method of Eilbott^{20a} and von Bergmann,^{20b} an injection of 50 mg. of bilirubin is given and the bilirubin content of the blood is measured five minutes, one hour, two hours and three hours after the injection. The normal retention is less than 15 per cent after three hours.

14 Malloy, H. T., and Evelyn, K. A. Oxidation Method for Bilirubin Determinations in Bile and Meconium with the Photo-Electric Colorimeter, *J Biol Chem* **122** 597, 1938.

15 Wallace, G. B., and Diamond, J. S. The Significance of Urobilinogen in the Urine as a Test for Liver Function, *Arch Int Med* **35** 698 (June) 1925.

16 Watson, C. J. The Average Daily Elimination of Urobilinogen in Health and in Disease, with Special Reference to Pernicious Anemia, *Arch Int Med* **47** 698 (May) 1931.

16a Terwen, A. J. L. Ueber ein neues Verfahren zur quantitativen Urobilinbestimmung in Harn und Stuhl, *Deutsches Arch f klin Med* **149** 92, 1925.

17 Furth, O., and Singer, K. Ueber die quantitative Bestimmung kleiner Urobilinogen- und Urobilinmengen in den Faeces, *Ztschr f d ges exper Med* **69** 152, 1929.

18 Bauer, R. Ueber alimentare Galaktosurie, *Deutsche med Wchnschr* **34** 1505, 1908.

19 Rosenthal, S. M., and White, E. C. Clinical Application of the Bromsulphalein Test for Hepatic Function, *J A M A* **84** 1112 (April 11) 1925.

20 (a) Eilbott, W. Funktionsprüfung der Leber mittels Bilirubinbelastung, *Ztschr f klin Med* **106** 529, 1927. (b) von Bergmann, G. Zur funktionellen Pathologie der Leber insbesondere der Alkohol-Aetiologie der Cirrhose, *Klin Wchnschr* **6** 776, 1927.

*Weltmann Test*²¹—Serum is diluted 1:50 with solution of calcium chloride in concentrations ranging from 0.1, 0.09, 0.08 to 0.01 per cent and then is heated in a water bath at 100 C for fifteen minutes. Normally, coagulation of the diluted serum occurs only in the first six or seven dilutions. Coagulation of the serum in the higher dilutions occurs in the presence of cirrhosis of the liver, hepatitis and occasionally various other conditions associated with hypoproteinemia.

REPORT OF CASES OF FAMILIAL NONHEMOLYTIC JAUNDICE

Ro Family—1 Arthur, aged 20, of Jewish origin, consulted one of us (W. D.) in March 1939 because of icterus.

The patient's paternal grandfather had been known to have jaundice for many years and had been studied for this condition at several hospitals. He died at the age of 64. The patient's father, who died of pneumonia at the age of 28, had also been known to have mild jaundice for several years, no records of the type of jaundice are available. The patient's mother was healthy. An only brother was said to be free of jaundice.

The mother stated that the patient was not jaundiced at birth. Jaundice had first been noted at the age of 4, directly after an operation for appendicitis. Since then jaundice had been constantly present. Subjective complaints were few, although the patient frequently felt tired and without "pep." He seemed unable to gain weight. The jaundice was variable in intensity and was perhaps somewhat increased by ingestion of fried and fatty foods.

Examination revealed a thin boy with moderate icterus of the scleras and the skin. Hepatic dulness began in the fourth right interspace and extended to the costal margin, the edge of the liver was not felt. Splenic dulness was not increased, and the edge was not palpable on deep inspiration. The remainder of the examination showed nothing abnormal.

The urine showed no bilirubin, and the urobilinogen content (Wallace-Diamond technic) was 1:20 on three occasions and 1:40 on three others. The stools were brown but definitely low in their content of urobilinogen. The icterus index was elevated (35 to 60 units), and there was a well marked increase in bilirubin which gave the "indirect" van den Bergh reaction. The total cholesterol of the blood measured 145 mg per hundred cubic centimeters and the cholesterol esters 101 mg. The blood proteins were normal in amount.

The blood was essentially normal. There was a slight increase in hemoglobin and in the red cell count. The reticulocyte count in seven examinations was 0.0, 0.0, 0.5, 0.2, 0.2, 0.0 and 0.0 per cent. The fragility of the red cells to hypotonic solutions of sodium chloride was 0.46 to 0.24 per cent. Their fragility to lysolecithin was normal. The average diameter of the red cells was 6.9 microns, the mean cell volume 88.9 cubic microns and the mean cell thickness 2.3 microns. Spherocytosis was completely absent, and the red cells, in all fresh preparations, including those showing rouleaux, were of normal thickness.

A sternal puncture revealed a normal cellular marrow. The ratio of nucleated red cells to granulocytes was 0.53 to 1. There was no evidence of erythroblastic hyperplasia or immaturity. The differential count of 500 marrow cells showed

²¹ Weltmann, O. Ueber die Spiegelung exsudativ-entzündlicher und fibroser Vorgänge im Blutserum, *Med. Klin.* **1** 240, 1930. Rosegger, H. Das Weltmann'sche Koagulationsband, *Ergebn. d. inn. Med. u. Kinderh.* **57** 183, 1939.

erythrocytes 0.4 per cent, normoblasts A 1.8 per cent, normoblasts B 11.2 per cent, normoblasts C 22.4 per cent, myeloblasts 2.6 per cent, myelocytes 10.2 per cent, metamyelocytes 22.6 per cent, mature polymorphonuclear leukocytes 17.6 per cent, eosinophils 8.4 per cent, basophils 0.2 per cent, and histiocytes 1.6 per cent.

The liver function tests gave negative results. The galactose tolerance test showed a total excretion of 2.3 Gm in four hours. The bromsulphalein test showed 4 per cent retention of dye after thirty minutes. Gastric analysis revealed a maximum concentration of 32 units of free hydrochloric acid. The concentration of bilirubin in the duodenal drainage was 14.7 mg per hundred cubic centimeters (normal), no cholesterol or other abnormal crystals were seen. Roentgenograms of the gallbladder and of the gastrointestinal tract were entirely normal.

Continued observation of this patient has revealed that he has constant, although somewhat intermittent, icterus. No change in icterus occurred with a fat-free diet or after the administration of sodium dehydrocholate by mouth.

2 Jerome, aged 18 (only sibling of Arthur), was completely asymptomatic. On examination, questionable icterus of the scleras was observed. The icterus index was 15, and quantitative determination of bilirubin gave 1.61 mg per hundred cubic centimeters. The remainder of the laboratory data are summarized in table 1.

Ru Family—Nancy (L) was the first member of the family to be observed. In 1936 she was said to have mild congenital hemolytic icterus. At that time studies were also made of two sisters, Susie and Josephine, but because our interest in hemolytic icterus was then only slight, no extensive investigations were carried out. In 1939 all the members of the family were recalled and systematic studies were undertaken.

The Ru family was of Italian origin, the father and mother having come to the United States in 1910. The family consisted of the parents and 8 children, 3 boys and 5 girls.

1 Lawrence Sr, the father, aged 59, was a farmer. He remembered that his mother was "yellow" and that her eyes were always "yellow." He was not certain about yellow coloration in any of his brothers or sisters. A first cousin, the son of Mario S, a maternal uncle (see page 270), was always yellow, as was the cousin's son. When Lawrence Sr was 18 it was remarked that his face had a peculiar yellow color. At 30 he was said to have "liver trouble," his face was "all green" for "about a year" and he had abdominal pain. He believed that since then his color had been normal. For about seven or eight years he had known that he had hypertension. In the fall of 1937 transient left hemiplegia had occurred. At the time of this writing he felt well. Examination revealed a healthy-appearing, well developed and well nourished man with definite icterus of the scleras and the skin. Hepatic dulness was noted from the fourth right interspace to the costal margin, the edge of the liver was not felt. Splenic dulness was not increased, the edge of the spleen was not palpable. The remainder of the examination revealed nothing abnormal except for slight hypertension with a pressure of 174 systolic and 90 diastolic. There was no modification of the icterus by the administration of tablets of dehydrocholic acid.

The laboratory data are summarized in table 1. The results of the bilirubin excretion test indicated a grossly pathologic condition, 64 per cent retention being observed at the end of three hours (fig 1).

2 John, aged 28, was born in the United States. He had had slight attacks of nausea and vomiting every five or six months, usually after a drinking bout, otherwise he was healthy. Definite icterus of the scleras and questionable icterus

TABLE 1—Laboratory Data in Cases of Nonhemolytic and Hemolytic Jaundice

Name	Hemoglobin (Evelyn)		Red Blood Cells	White Blood Cells	Platelets	Reticulo cytes, per Cent	Hemato crit Readings, per Cent	Mean Corpuscular Volume, Cubic Microns	Mean Corpuscular Diameter, Microns	Mean Corpuscular Thickness, Microns	Sphero cytic Index (Normal, 0.25 to 0.31)	Fragility		Blood Bilirubin		Fecal Urobilinogen, Mg
	Per Cent	Gm										Sodium Chloride	Lyso lecithin	Icterus Index	Quantitative, Mg per 100 Cc	
Familial nonhemolytic jaundice																
Ro																
Arthur	109	17.0	5,830,000	10,000	573,800	0.2	52.0	88.9	6.9	2.3	0.33	0.16 to 0.24	Normal	35.0 to 60.0	5.2 to 13.1	18.0
Jerome	104	16.2	5,850,000	11,300	514,800	0.7	50.0	85.1	7.0	2.2	0.31			15.0	1.61	
II Familial nonhemolytic jaundice																
Ru																
Lawrence Sr	99	15.3	4,600,000	8,100		0.2	47.0	102.0	7.0	2.6	0.37	0.14 to 0.20	Normal	18.0	2.14	63.0
Lawrence Jr	93	14.5	5,060,000	4,800		0.2	44.0	86.9	6.8	2.3	0.34	0.12 to 0.24	Normal	20.0	1.87	16.0
John	100	15.6	5,270,000	7,000		0.0	16.0	87.2	7.0	2.2	0.31	0.42 to 0.21	Normal	15.0	1.41	
Tony	95	14.8	4,530,000	4,800		0.0	46.5	102.0	6.9	2.7	0.39	0.11 to 0.24	Normal	18.0	1.41	58.5
Josephine	93	14.4	4,660,000	7,900	396,100	0.2	41.0	87.9	7.1	2.2	0.31	0.14 to 0.30	Normal	20.0	3.04	53.0
Susie	84	13.1	4,020,000	6,100	313,500	0.4	38.0	94.5	7.3	2.2	0.30	0.18 to 0.24	Normal	15.0 to 25.0	2.45	50.0
Mary	80	12.5	4,000,000	6,000	776,000	1.3	36.5	91.0	7.1	2.2	0.31	0.42 to 0.24	Normal	20.0	2.90	34.0
Nancy (L.)	89	13.8	4,350,000	8,800	504,000	1.1	39.5	90.8	7.1	2.3	0.33	0.41 to 0.24	Normal	17.5	1.83	44.0
Caroline	84	13.1	4,530,000	9,800		0.4	10.0	88.3	7.6	1.97	0.26	0.42 to 0.24	Normal	6.0	0.79	34.0
III Familial hemolytic jaundice																
Lawrence N																
	112	17.5	5,360,000	7,800	900,000	0.5 to 4.6	46.0	85.5	6.8 to 7.1	2.4 to 2.6	0.31	0.56 to 0.16	Increased	35.0	3.2 to 5.4	140.0
Robert B																
	97	15.1	4,720,000	8,100	405,000	1.3 to 5.0	42.0	87.9	6.9	2.3	0.33	0.52 to 0.20	Increased	11.0	0.7	430.0

of the skin were observed. Hepatic dulness was somewhat increased and the edge of the liver was just palpable. The spleen was not felt.

3 Tony, aged 26, was born in the United States. He had had pneumonia in childhood and scarlet fever at the age of 10, but had no complaints at the time of study. He was a healthy-appearing man with slight, though distinct, icterus of the scleras and the skin. There was no enlargement of the liver or the spleen.

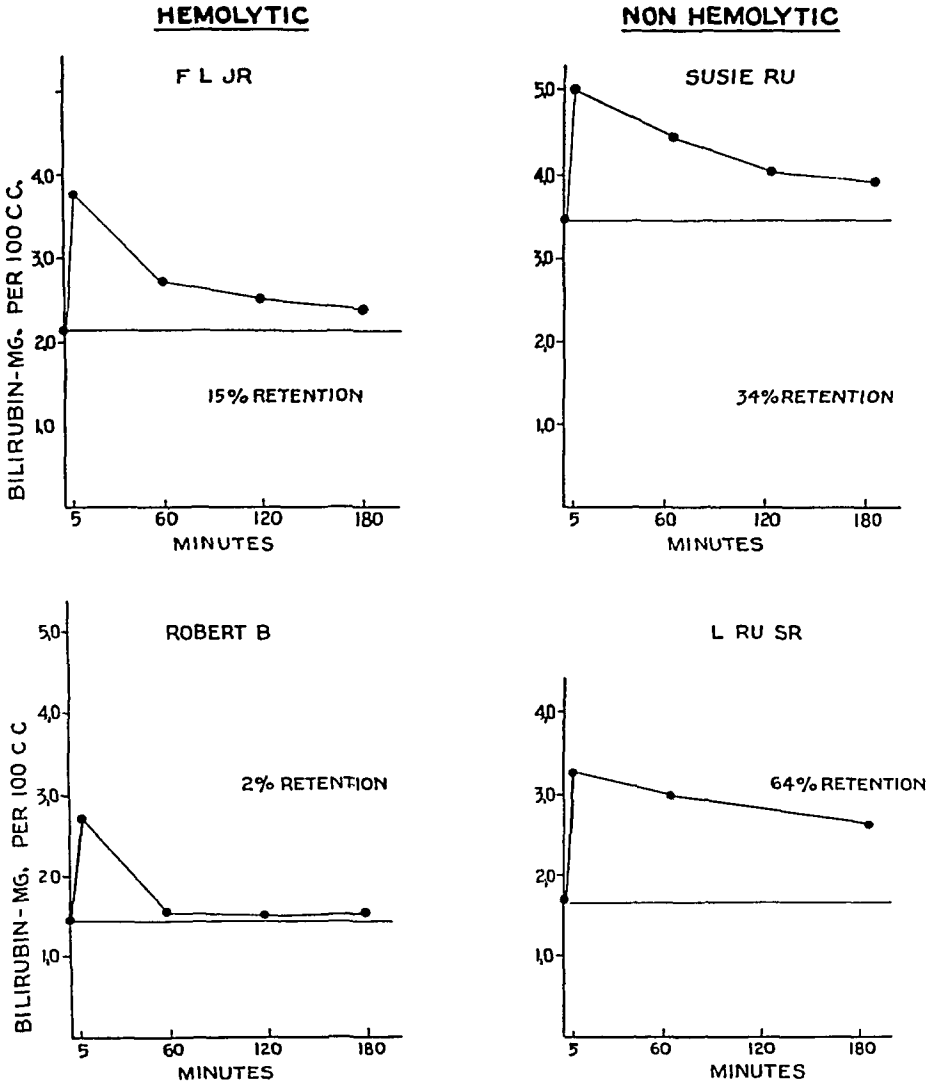


Fig 1—The results of the bilirubin excretion test in 2 patients with familial hemolytic icterus as compared with results in 2 patients with the nonhemolytic variety. Note that the bilirubin retention in the former patients is normal, although approximately the same degree of bilirubinemia is present in the two groups of patients.

4 Lawrence Jr, aged 16, was born in the United States. His past history was normal, and he had no complaints at the time of study. He was a healthy-appearing boy with definite icterus of the skin and scleras. Enlargement of the liver or the spleen was not detected by percussion or palpation.

In general, the male members of the family had not noticed icterus (except for the father, years previously) and felt well. They were uncooperative in the investigations. The female members had apparently paid more attention to themselves, knew of their yellowish coloration and usually complained of fatigue, lack of energy and occasional headaches. They were far more amenable to investigative studies.

5 Nancy, aged 27, complained of fatigue and exhaustion in May 1936. At first she stated that for about ten years occasional changes in the color of her face had been noted by her companions, at a later visit she stated that she had found that her jaundice had been noted since birth and had been intermittent. After the birth of her second child (by cesarean section), in 1934, she had failed to regain her normal vigor and complained of fatigue, dizziness, epigastric pain, headache and attacks of trembling, at times relieved by vomiting. After an attack, which might have had some relation to the menstrual cycle, she noticed that her skin became more yellow. Her appetite was poor, and various foods, such as pork, oranges and strawberries, caused gastric distress. Examination in May 1936 showed definite jaundice of the skin and the scleras. All further examinations revealed nothing abnormal, except for the icterus.

The laboratory data for Nancy are summarized in table 1. The icterus index varied from 18 to 23, the bilirubin content of the blood was approximately 2 mg per hundred cubic centimeters. The fragility test gave a value of 0.42 to 0.32 per cent in June 1936, 0.42 to 0.34 per cent in October 1936 (drop method) and 0.44 to 0.24 per cent in 1939 (method of Daland and Worthley). In 1936 the hemoglobin varied from 82 to 85 per cent (Sahli), the red cell count from 4,000,000 to 4,880,000 and the white cell count from 7,300 to 9,300. The reticulocytes were 2 per cent. Biopsy of the bone marrow of the sternum (trephine method) yielded essentially normal findings, with no evidence of erythroblastic hyperplasia. The urine was normal. The cholesterol content of the blood was 202 mg per hundred cubic centimeters. The Hinton and Kahn reactions were negative. Roentgenograms of the gallbladder were normal. A series of roentgenograms of the gastrointestinal tract showed nothing abnormal except an inconstant pressure defect on the superior surface of the duodenal cap. Special hematologic studies in 1939 (when the patient was three months pregnant) showed normal values for hemoglobin and normal erythrocyte, leukocyte and thrombocyte counts. The reticulocyte value was 1.1 per cent. The average diameter of the red cells was 7.1 microns, with a variation in size from 5.3 to 9.0 microns. The mean corpuscular volume was 90.8 cubic microns, the mean cell thickness 2.3 microns and the spherocytic index 0.33. The resistance to hypotonic solutions of sodium chloride was 0.44 to 0.24 per cent, the fragility to lysolecithin was normal, the blood bilirubin gave an indirect reaction, there was no increase in the urinary urobilinogen, and the urobilinogen content of the feces was 44 mg per day (normal value, 40 to 150 mg).

6 Susie, aged 20, in October 1936 complained of headaches, dizziness, fatigue and constipation. At another time she stated that since the age of 15 she had noted a yellowish coloration of the skin and eyes, which she believed became aggravated with excitement, nervousness, fatigue and eating fried and fatty food and chocolate. A physical examination showed nothing abnormal except for perceptible icterus of both the skin and the scleras.

The patient was restudied in 1939. The laboratory data are summarized in table 1. The values for hemoglobin and the erythrocyte, leukocyte and platelet counts were essentially normal in April 1939, although in July and August 1939 there was evidence of slight normocytic anemia (hemoglobin 75 per cent, red cell

count 3,780,000) The reticulocyte count was 0.2, 0.2 and 0.4 per cent The mean diameter of the red blood cells was 7.3 microns, the mean cell volume 94.5 cubic microns, the mean cell thickness 2.2 microns and the spherocytic index 0.30 The thickness measured directly from rouleaux was 2.1 microns, and the photomicrographs of rouleaux showed normal cells, with no tendency toward increased thickness The fragility of the red cells to hypotonic solutions of sodium chloride was 0.48 to 0.24 per cent, the fragility to lysolecithin was normal The urine showed no increase in urobilinogen, the icterus index of the blood varied from 15 to 25 units and the bilirubin content of the blood was 2.45 mg per hundred cubic centimeters The urobilinogen content of the feces was 50 mg per day The bromsulphalein test for hepatic function showed a 2 per cent retention after thirty minutes (normal)

7 Josephine, aged 23, had always considered herself well except for frequent fatigue and lack of "pep," together with noticeable sallowness Examination dis-

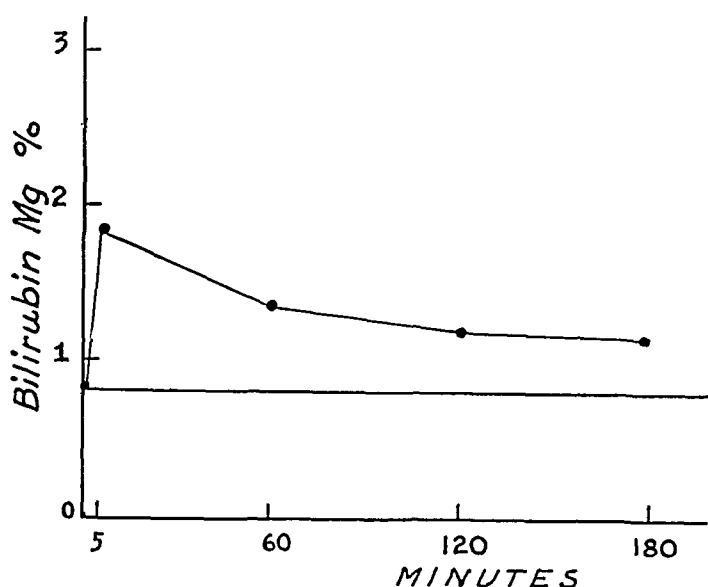


Fig 2—Result of the bilirubin excretion test in Caroline Ru, the only one of the Ru children without definite bilirubinemia At the end of three hours there is 33 per cent retention of injected bilirubin (normal retention up to 15 per cent), despite the absence of icterus

closed slight icterus of the scleras and a sallow appearance of the skin Neither the liver nor the spleen was palpable The laboratory data are recorded in table 1

8 Mary, aged 19, also felt tired from time to time Examination revealed nothing abnormal except for slight icterus of the scleras and the skin The laboratory data are recorded in table 1 The result of the bromsulphalein excretion test was normal

9 Caroline, aged 25, felt well except for slight asthenia On examination she seemed somewhat more vigorous and robust than her sisters There was no icterus of the scleras, and the skin did not present the sallow, yellowish appearance of her sisters Although the bilirubin content of the serum was within normal limits (0.79 mg per hundred cubic centimeters), the response to the bilirubin excretion test was definitely, though slightly, pathologic, since only 66 per cent of the injected bilirubin was excreted after three hours (normally 85 per cent is excreted)

ANALYSIS OF CASES, INCLUDING THOSE IN THE LITERATURE

Onset of Disease—This cannot ordinarily be ascertained, although patients or their relatives will occasionally date the onset of the jaundice by some specific event, such as an operation (Arthur Ro) or an illness (Lawrence Ru Si). Rozendaal and his associates reported several cases in which jaundice had been observed at birth and had been constantly present until adult life.

Familial Character—This has been stressed by Tecon, who stated that one must discriminate between two types of hereditary hyperbilirubinemia "familial cholemia" and hemolytic icterus. He reported on 2 families, family C₁, 2 members, and family G, 3 members. It should be stated that the record of family Cr is not convincing, since the only abnormality observed in "Maurice" of this family was a bilirubin content of the blood of 0.85 mg per hundred cubic centimeters, his brother Pierre's bilirubin content varied from 1.06 to 1.5 mg. The early descriptions of Gilbert and his associates dealing with "familial cholemia" were in all probability, as stated previously, those of mild congenital hemolytic icterus. Van den Beigh, in his description of "physiologic hyperbilirubinemia," stated that he had observed a case of familial occurrence. Rozendaal, Comfoit and Snell, in analyzing 214 cases of mild icterus, found 34 instances in which the disease could be classified as "constitutional hepatic dysfunction." From the patients in several of these cases a familial history of icterus was obtained, although the other members of the family were not examined. In 1 case which was cited, a man aged 32 had "always" been slightly jaundiced, his mother, 5 brothers and 1 sister were similarly affected, although otherwise in good health (hematologic and chemical details were not given). In Meulengracht's series of 24 cases, icterus was present in 3 members of 1 family, and either a brother or a sister of the patients in 2 other cases was also said to have icterus. (Laboratory data were not given.)

The method of transmission in these cases can only be speculated on, since so few cases have been described. In both our families transmission was through the father. However, the elder Ru's mother was probably the transmitter, and his sister had apparently transmitted the condition to her son. The mother was also apparently the transmitter in 1 of the cases of Rozendaal and his associates. It would seem, therefore, that both parents may transmit the disease directly to their children. Of the 8 children in the Ru family, all were affected (Caroline only slightly), this might indicate that the disorder was transmitted as a mendelian dominant character.

Age, Sex, Social Status and Race—Meulengracht stressed the juvenile character of the condition ("icterus intermittens juvenilis") and stated that in time it might disappear. In 1 of the cases reported

by Rozendaal and his collaborators, the mother of a patient aged 32 had shown continued icterus to the time of the report. Although the great majority of our patients were between 20 and 25 years of age, 1, Lawrence Ru Sr, was 60. The latter's first cousin, aged 51, was also definitely icteric. In the Ro family, the father of the 2 boys studied had been known to have jaundice, while the grandfather had been jaundiced for many years at the time of his death, at the age of 64.

Both sexes appear to be similarly affected. Although Meulengracht observed the condition most commonly in members of the medical profession, the apparent frequency of occurrence, as he pointed out, might have been due to the more careful observation of slight abnormalities by members of this group. Our own cases occurred in families without medical associations. With reference to racial occurrence, the disorder has been described from France,¹ Switzerland,⁶ Holland,³ Denmark⁴ and this country.⁵ In our own cases, the Ru family was of Italian origin and the Ro family was Jewish.

Symptoms—Meulengracht⁴ stated that the histories of all patients with this type of jaundice showed an "extraordinary monotony" characterized by fatigue and asthenia. The periods of fatigue were usually consistent with periods of increased jaundice. In our own cases, the same "monotony" of symptoms was present in both the Ro and the Ru family, although not as a constant feature. In the Ro family, 1 member, who was perceptibly jaundiced, frequently felt tired and without "pep", the other, who was subicteric, had no symptoms. In the Ru family, the symptoms of frequent fatigue, gastric distress and asthenia were limited to the female members. It is possible that these symptoms were chiefly neurasthenic in origin and completely unrelated to the icterus. The male members of the family, although having the same degree of icterus, were completely asymptomatic and able to do heavy manual work.

Physical Signs—Except for icterus, the results of physical examination were essentially normal. The icterus varied in intensity from patient to patient and in the same person from time to time. In most of the members of the Ru family the icterus was discernible only when the scleras were exposed (subicterus), in Susie, and at times in Nancy, the jaundice was, however, apparent at a glance. This was the case in Arthur Ro, the latter's brother, Jerome, however, showed only icterus of the scleras. It is apparent that most cases are, in all likelihood, missed because of the slight degree of icterus present, many persons are thought merely to have a "sallow" complexion or "anemia". Our own patients were, for the most part, considered a little sallow or pallid but otherwise normal. The edge of the liver was occasionally felt. We

were unable to feel the edge of the spleen in any of our patients, nor was the splenic dullness increased to percussion. No other abnormal physical findings were discovered.

Laboratory Data—The most important laboratory finding, and of course a prerequisite in the diagnosis, was the bilirubinemia. This was usually moderate, the amount of bilirubin ranging in the Ru family from 1.41 to 3.07 mg per hundred cubic centimeters with an associated icterus index of 15 to 25. In the case of Arthur Ro the bilirubin level was distinctly above the subicterus level and ranged from 5.2 to 13.1 mg per hundred cubic centimeters, with an associated icterus index of 35 to 60 units. However, this patient's brother had icterus indexes corresponding to those in our least jaundiced patients: icterus index 15, bilirubin level 1.61 mg per hundred cubic centimeters. Most of the patients in Meulengracht's 24 cases had a slight degree of icterus, 13 of them presenting an icterus index between 10 and 15 units. Only 3 had icterus indexes between 20 and 25 units. In the cases reported by Tecon the icterus was also extremely mild, with the bilirubin levels ranging from 0.85 to 1.6 mg per hundred cubic centimeters. Of the cases cited by Rozendaal and his co-workers, the bilirubin level in 1 varied from 2.8 to 3.4 mg and in another from 3.4 to 4.2 mg per hundred cubic centimeters. The bilirubin was always of the "indirect" variety.

Examination of the urine was uniformly negative for bilirubin and for increased amounts of urobilinogen.

Blood In our cases the hematologic findings were essentially normal as regards the values for hemoglobin and the erythrocyte, leukocyte, thrombocyte and reticulocyte counts. For the Ro boys the hemoglobin content, the erythrocyte counts and the hematocrit levels were at high normal values. In the Ru family the women had red blood cell counts which were at low normal values—from 3,670,000 to 4,660,000—and the hemoglobin concentrations ranged from 76 to 93 per cent. The Ru men also had low normal red cell counts (for men), ranging from 4,530,000 to 5,270,000. Despite the slight tendency to anemia in this family, the hemoglobin values were for the most part normal, this normality resulted in a color index just above 1 in several instances. The hematocrit-red cell relationship (mean corpuscular volume) was within the normal range, 85.4 to 94.5 cubic microns in all cases except 2, in which there was a possible increase (102 cubic microns). The only possible hematologic abnormality which could be ascertained in our cases was a distinct tendency to microcytosis, since the diameter of the red cells ranged from 6.8 to 7.3 microns in dry stained films. This observation was repeatedly checked. The coexistence of erythrocytes somewhat smaller than normal and a normal mean corpuscular volume

should indicate a mean corpuscular thickness which is either at the upper limit of normal or just above it. However, careful measurements of thickness made directly from rouleaux in these cases, together with the study of rouleaux from photomicrographs, failed to show any evidence of increased thickness. In fact, the red cells in photomicrographs of rouleaux seemed at times somewhat thinner than normal. The possible inaccuracy of the measurements for "mean corpuscular thickness" and of the "spherocytic index" as derived from the red cell count, the hematocrit readings and the mean cell diameter has been commented on by Price-Jones, Vaughan and Goddard,²² Ponder²³ and Barrett.²⁴ These measurements are based on the postulate that the red cell is a short cylinder, whereas it is actually a biconcave disk. The earlier investigators presented as normal limits for thickness 1.729 to 2.545 microns. The measurements of thickness in our cases fall well within this range. The association of definite, though slight, microcytosis with a normal cell volume in our cases is difficult to explain. In view of our observations made directly on fresh preparations of blood, we are, however, inclined to disregard borderline figures obtained for the mean corpuscular thickness by the indirect method.

The resistance of the red cells to hypotonic solutions of sodium chloride was normal in every patient tested, since this test may be considered an indirect measurement of red cell thickness, the normal findings tend to confirm the absence of increased thickness. In cases of congenital hemolytic icterus with similar values for corpuscular thickness (table 1) the result of the fragility test is definitely abnormal. No evidences of increased regenerative activity on the part of the marrow were present in any case, since the leukocyte, granulocyte, platelet and reticulocyte counts always were well within the normal limits.

The hematologic findings in the few cases reported in the literature were within normal limits, although complete reports were not usually given. Meulengracht stated that the mean diameter of the red cells in his cases was normal, varying between 7.8 and 8.0 microns as determined by measurement of the fresh red cells in their own plasma. However, Gripwall,²⁵ in a recent study using the same method, stated that normal values range from 8.2 to 8.6 microns, with an average value

22 Price-Jones, C., Vaughan, J. M., and Goddard, H. M. Hematological Standards of Healthy Persons, *J. Path. & Bact.* **40**: 503, 1935.

23 Ponder, E. The Mammalian Red Cell and the Properties of Haemolytic Systems, in Chambers, R., and others. *Protoplasma-Monographien*, Berlin, Verlagsbuchhandlung Gebrüder Borntraeger, 1934, vol. 6.

24 Barrett, A. M. A Special Form of Erythrocyte Possessing Increased Resistance to Hypotonic Saline, *J. Path. & Bact.* **46**: 603, 1938.

25 Gripwall, E. Zur Klinik und Pathologie des hereditären hämolytischen Ikterus, *Acta med. Scandinav.*, 1938, supp. 96, p. 1.

of 84 microns. This might indicate that the cells in Meulengracht's cases, as in our own, were somewhat smaller than normal.

Bone Marrow—Specimens for biopsy were taken in 2 of our cases, and the observations were all within normal limits. There was no evidence of erythroblastic hyperplasia, and the relationship of the nucleated red cells to the white cells was normal.

Stools—Most accounts of the disorder have failed to mention the appearance of the stools. The important matter of the urobilinogen excretion has, furthermore, never been studied. In our cases the stools were always of a normal brown color. The daily excretion of urobilinogen was always either normal or somewhat diminished.

Liver Function Tests—When performed, the galactose tolerance and bromsulphalein tests yielded normal results. The Weltmann reaction was also normal (coagulation up to seven dilutions) in all the patients tested. The reaction to injected bilirubin was abnormal, excretion was greatly delayed, and the resultant retention of bilirubin three hours after injection was thus much greater than the high normal value of 15 per cent. Of great interest was the presence of a slightly abnormal curve in 1 of the patients (Caroline Ru), indicating a possible latent tendency toward biliubinemia, although this condition was not present.

Prognosis—From the standpoint of the person's general health the condition appears to have but little significance. Chauffard's remark concerning patients with familial hemolytic icterus seems even more apt for patients with the nonhemolytic type: "The patient is more icteric than sick." That the father of the Ru family presented no greater degree of icterus than his children points to the benign, nonprogressive character of the disorder. It is possible, however, that examples of more severe forms of the disease will be found and that in these the evidences of progressive hepatitis will be present.

Treatment—Treatment with low fat diets and with choleretics (sodium dehydrocholate) in 2 cases failed to make any impression on the jaundice. More drastic forms of treatment of such a mild disorder did not appear to be indicated.

COMMENT

There are two aspects of this problem which are worthy of comment. (1) Can one be certain that the condition described is a well defined syndrome, clearly to be differentiated from familial hemolytic icterus and chronic mild hepatic disease? (2) Assuming the existence of such a disease entity, what are the possible pathologic mechanisms involved?

Is Familial Nonhemolytic Icterus a Well Defined Syndrome?—Familial icterus is ordinarily assumed to be hemolytic. That a non-hemolytic variety exists is usually not recognized. Numerous studies on

cases of both types of familial icterus have led us to conclude that they can be clearly differentiated

A Differentiation from Familial Hemolytic Icterus In the presence of chronic slight icterus in which the blood bilirubin is of the "indirect" variety, the diagnosis of mild or latent hemolytic icterus is

TABLE 2—*Comparison of Two Patients with Hemolytic Icterus and Nonhemolytic Icterus and Approximately the Same Level of Bilirubin, Percentage of Hemoglobin and Number of Red Cells*

	Lawrence N (Hemolytic Icterus), Aged 28	Arthur R (Familial Nonhemolytic Icterus) Aged 21
Family history	Nothing abnormal	Grandfather, jaundice, father, jaundice, brother, slight jaundice
Past history	Rheumatic fever, rheumatic heart disease	Appendectomy at 3
Present illness	Anorexia, fatigue, jaundice noticed by friends	Weight below normal no symptoms jaundice noticed by friends
Physical examination	Icterus, spleen palpable 3 finger breadths	Icterus, spleen not felt
Blood picture	Hemoglobin, 110 per cent Red blood cells, 5,700,000 White blood cells, 8,200 Platelets, 610,000 †Reticulocytes, 0.5, 2.7, 4.6, 0.8, 1.2 % Hematocrit reading, 45, 46, 48, 46% Mean corpuscular volume, 83 to 94 cubic microns Mean corpuscular diameter, 6.8 to 7.1 microns Mean corpuscular thickness, 2.1 to 2.6 microns †Fragility of the red blood cells to hypotonic solutions of sodium chloride, 0.72 to 0.04, 0.50 to 0.16, 0.48 to 0.16, 0.56 to 0.16 per cent †Fragility of the red blood cells to lysolecithin positive †Rouleaux, thick cells †Stained smear, spherocytosis †Wet isotonic preparations, "cups" common	Hemoglobin, 100 per cent Red blood cells, 5,730,000 White blood cells, 10,000 Platelets, 573,000 Reticulocytes, 0.0, 0.0, 0.5, 0.2, 0.2, 0.0, 0.0 % Hematocrit reading, 52, 56, 54% Mean corpuscular volume, 91 to 98 cubic microns Mean corpuscular diameter, 6.9 to 7.0 microns Mean corpuscular thickness, 2.3 to 2.5 microns Fragility of the red blood cells to hypotonic solutions of sodium chloride 0.46 to 0.24, 0.44 to 0.24, 0.46 to 0.20, 0.42 to 0.20 per cent Fragility of the red blood cells to lysolecithin normal Rouleaux normal Stained smear, no spherocytes Wet isotonic preparations, no "cups"
Other laboratory data	Icterus index, 35, 40, 38 units Bilirubin, 5.4, 3.2 mg per 100 cc Van den Bergh reaction indirect Urine, bile absent Urobilinogen, 1.40, 1.80, 1.20 †Stool, urobilinogen, 440.0 mg †Bone marrow, hyperplasia of red blood cells	Icterus index, 35, 50, 50, 60, 45 units Bilirubin, 10.8, 5.2, 9.6, 13.1 mg per 100 cc Van den Bergh reaction indirect Urine, bile absent Urobilinogen, 1.40, 1.20, 1.20, 1.20 Stool, urobilinogen, 18 mg Bone marrow, normal

† An important differential point

usually made even in the absence of a positive family history, splenomegaly, anemia, spherocytosis, an increased fragility of the red cells to hypotonic solutions of sodium chloride, reticulocytosis and an increased output of urobilinogen in the urine. Gansslen²⁶ described cases of the "latent" form in which many of these symptoms were

26 Gansslen, M. Die hamolytische Konstitution, Klin. Fortbild. 4: 607, 1936, Der hamolytische Ikterus, hamolytische Konstitution, Klin. Wchnsch. 6: 929, 1927.

absent, for example, in 10 per cent of his cases the red blood cells showed a normal fragility to hypotonic solutions of sodium chloride, and in 30 per cent the spleen could not be palpated. That cases of very

TABLE 3—*Differentiation of Familial Hemolytic, Familial Nonhemolytic and Hepatic Jaundice*

Signs and Symptoms	Nonhemolytic Jaundice	Latent Hemolytic Jaundice	Manifest Hemolytic Jaundice	Slight "Liver Damage," Slight Parachymatous Jaundice	Fully Developed Hepatic Disease and Hepatic Jaundice
Familial history of jaundice	Present	Present	Present	Absent	Absent
Size of liver (palpation)	Slight to moderate	Absent or slight	Moderate	Slight	Distinct
Size of spleen (palpation)	Normal	Normal	May be enlarged	May be normal	May be enlarged
Bilirubin in urine	Normal	Usually palpable	Readily palpable	May not be enlarged	May be readily palpable
Urobilinogen in urine	Absent	Absent	Absent	Usually absent except in serial examinations	Present
Anemia	Not increased	Usually increased, may be normal	Increased	Usually increased	May be absent (obstruction)
Spherocytosis of red cells	Absent	Absent	Present	Absent	Frequently present
Fragility of red cells	Absent	Present	Present	Absent	Absent
Reticulocytosis	Normal	May be only slightly increased	Increased	Normal	May be decreased
Hyperplasia of bone marrow	Absent	May be absent on single examination, always present on serial examinations	Present	Absent	Absent
Liver function tests	Absent	Present	Present	Absent	May be present if anemia is present
Feces	Results negative except for impaired bilirubin excretion	Results negative	Negative	May be negative	Positive (pathologic)
Color	Normal	Dark	Dark	Normal	Hypocholic
Urobilinogen content	Normal or diminished	Increased	Increased	Normal	Diminished
Bilirubin in blood	Increased, indirect van den Bergh reaction	Increased, indirect van den Bergh reaction	Increased indirect van den Bergh reaction	Increased may show indirect van den Bergh reaction	Increased direct van den Bergh reaction

mild congenital hemolytic icterus exist cannot be denied. However, even in these, one or several of the aforementioned symptoms are observed during the course of several examinations.

The following 2 cases of mild hemolytic icterus are illustrative.

Robert B, a medical student aged 24, had known of the presence of slight jaundice for many years. His father's father had been jaundiced, and his father had been jaundiced for many years. Of 3 siblings, a brother and sister were jaundiced.

Crises had never occurred in any member of the family, and none had required splenectomy. He was a rather thin, otherwise healthy-appearing young man with slight icterus of the scleras. The edge of the spleen was just felt at the costal margin. Laboratory data were as follows: hemoglobin concentration 97 per cent, red cell count 4,760,000 and white cell count 8,100, platelet count 405,000, reticulocyte count 13, 37, 40, 17, 19, 26, 44 and 39 per cent at successive observations, hematocrit reading 42 per cent, mean corpuscular volume 88 cubic microns, mean corpuscular diameter 69 microns, mean corpuscular thickness (indirect method) 23 microns and mean corpuscular thickness (direct method) 24 microns. Preparations of rouleaux showed definite increase in thickness with well defined individual variation. Fragility of the red cells to hypotonic solutions of sodium chloride was 0.52 to 0.20 per cent, fragility to lysolecithin was increased. No bilirubin or increased urobilinogen excretion occurred in the urine. The icterus index of the blood was 11 units, and the bilirubin content was 0.8 mg per hundred cubic centimeters. The daily urobilinogen excretion in the feces was 430 mg. The result of the bilirubin excretion test was normal, since 98 per cent of the injected dye was excreted in three hours.

Lawrence N., a 28 year old truck driver with an entirely normal family history, had rheumatic fever and rheumatic heart disease in 1932. While he was in the hospital at that time jaundice and splenomegaly were noted, and they have been present since. He was thin and definitely icteric. Examination of the heart revealed stenosis of the mitral valve. The edge of the spleen was felt 3 fingerbreadths below the left costal margin. Laboratory data were as follows: hemoglobin concentration 110 to 116 per cent (Evelyn), red cell count 4,810,000 to 5,700,000 and white cell count 4,900 to 8,200, platelet count 610,000 to 904,000, reticulocyte count 0.5, 27, 46, 0.8 and 12 per cent at successive observations, hematocrit reading, 45 to 48 per cent, mean corpuscular volume 83 to 94 cubic microns, mean corpuscular diameter 68 to 71 microns, mean corpuscular thickness 235 to 260 microns. The rouleaux were increased in thickness, stained smears showed typical spherocytes, the fragility to hypotonic solutions of sodium chloride was 0.72 to 0.04, 0.50 to 0.16, 0.48 to 0.16 and 0.56 to 0.16 per cent on various tests, fragility to lysolecithin was increased. The urine showed no bilirubin, urobilinogen concentration in the urine varied from 1.2 to 1.80. The icterus index of the blood varied from 35 to 40 units, the bilirubin content (indirect method) varied from 3.2 to 5.4 mg per hundred cubic centimeters. The result of the bilirubin excretion test was normal (5 per cent retention). The daily fecal urobilinogen content was 440.0 mg.

In the physical examination of patients with even mild hemolytic icterus, splenomegaly is almost always observed. Otherwise, except for icterus, no pathologic condition may be found. The hematologic findings are of great importance. Two sets of phenomena are to be looked for: (1) those indicating increased hemolytic activity and (2) those indicating increased regenerative activity on the part of the bone marrow. Indicators of increased hemolytic activity are: (1) normal or increased mean corpuscular volume accompanied by microcytosis, (2) increased mean corpuscular thickness, (3) increased thickness and varying degrees of spherocytosis as seen in rouleaux and in fresh isotonic preparations of blood and (4) increased fragility to hypotonic solutions of sodium chloride and to lysolecithin. We have found that

the direct examination of both fresh and stained preparations of blood is of greater value in cases of mild icterus than determination of the mean corpuscular thickness, since the latter may remain practically unaltered although the erythrocytes in fresh preparations of rouleaux



Fig 3—Photomicrographs of rouleaux ($\times 1,000$) in fresh preparations of blood A, normal person, normal rouleau formation, with a slight variation in thickness, B, R B, a patient with mild congenital hemolytic icterus, a red cell count of 4,800,000, variation in thickness of individual erythrocytes and a tendency toward increased thickness, C, Susie Ru, a patient with familial nonhemolytic icterus, well formed rouleaux and erythrocytes of normal thickness, some apparently even thinner than normal

and in stained preparations show the characteristic changes of increased thickness The test for fragility is of even greater importance, since

it frequently reveals abnormality when the figures for thickness are only insignificantly altered. A single examination for fragility may show no definite abnormality, in all cases at least 2 examinations should be made if possible. This was well brought out in the case of Lawrence N., who at different times showed readings which varied from essentially normal (0.48 to 0.16 per cent) to decidedly abnormal (0.72 to 0.04 per cent). The fragility of the red cells to lysolecithin—a lysin derived from normal serum—has been shown by Singer¹³ to be abnormal in cases of congenital hemolytic icterus, even when in very mild forms, the fragility to hypotonic solutions of sodium chloride was normal or questionable. This finding has been confirmed by Gripwall.²⁵ The red cells in 15 cases of familial hemolytic icterus were unusually fragile to solutions of lysolecithin, whereas in all our cases of nonhemolytic icterus in which the patient was examined fragility of the red cells to lysolecithin was normal.

Often just as important as the indicators of increased hemolytic activity are the indicators of increased regenerative activity on the part of the marrow. The latter are reticulocytosis, increased polychromatophilia, polymorphonuclear leukocytosis and thrombocytosis. Except in severe and moderately severe conditions, leukocytosis and thrombocytosis are not particularly evident, but even in the mildest form the reticulocyte count is found to be elevated, at least in serial observations.

Studies on Robert B. and Lawrence N., previously referred to, disclosed that there was great variability in the reticulocyte count, with the percentage varying widely from normal to decidedly abnormal values. On successive counts, abnormal values could always be demonstrated, quite in contrast to the findings in patients with nonhemolytic icterus in whom, even on repeated examinations, a significant elevation in the reticulocyte count was never demonstrated.

The urine in cases of hemolytic jaundice usually shows an increased content of urobilinogen, although normal values may be present even in moderate or severe forms of the disease. Of 30 cases reported by Gripwall,²⁵ the urobilinogen content of the urine was normal in about one-third. This circumstance was also reported by Watson^{26a} and by Barker^{26b}. In the cases of nonhemolytic jaundice the content of urobilinogen in the urine was always within normal limits. The outstanding differential

26a Watson, C. J. Studies of Urobilinogen. II. Urobilinogen in the Urine and Feces of Subjects Without Evidence of Disease of the Liver or Biliary Tract, *Arch Int Med* **59** 196 (Feb.) 1937, III. The Per Diem Excretion of Urobilinogen in the Common Forms of Jaundice and Disease of the Liver, *ibid* **59** 206 (Feb.) 1937.

26b Barker, W. H. Excretion of Bile Pigment and Hepatic Function in Diseases of the Blood, *Arch Int Med* **62** 222 (Aug.) 1938.

feature was the content of urobilinogen in the feces. In 7 cases of congenital hemolytic jaundice, including even the mildest or most latent variety (cf Robert B), the daily urobilinogen excretion in the feces was always elevated from 400 to 800 mg. In the cases of nonhemolytic jaundice, on the other hand, the urobilinogen content was either normal or somewhat reduced.

Studies of the urobilinogen content of the feces have not previously been made in instances of familial nonhemolytic icterus. The contrast between the high values obtained for the patients with hemolytic jaundice and the normal or even low values obtained for the patients with non-

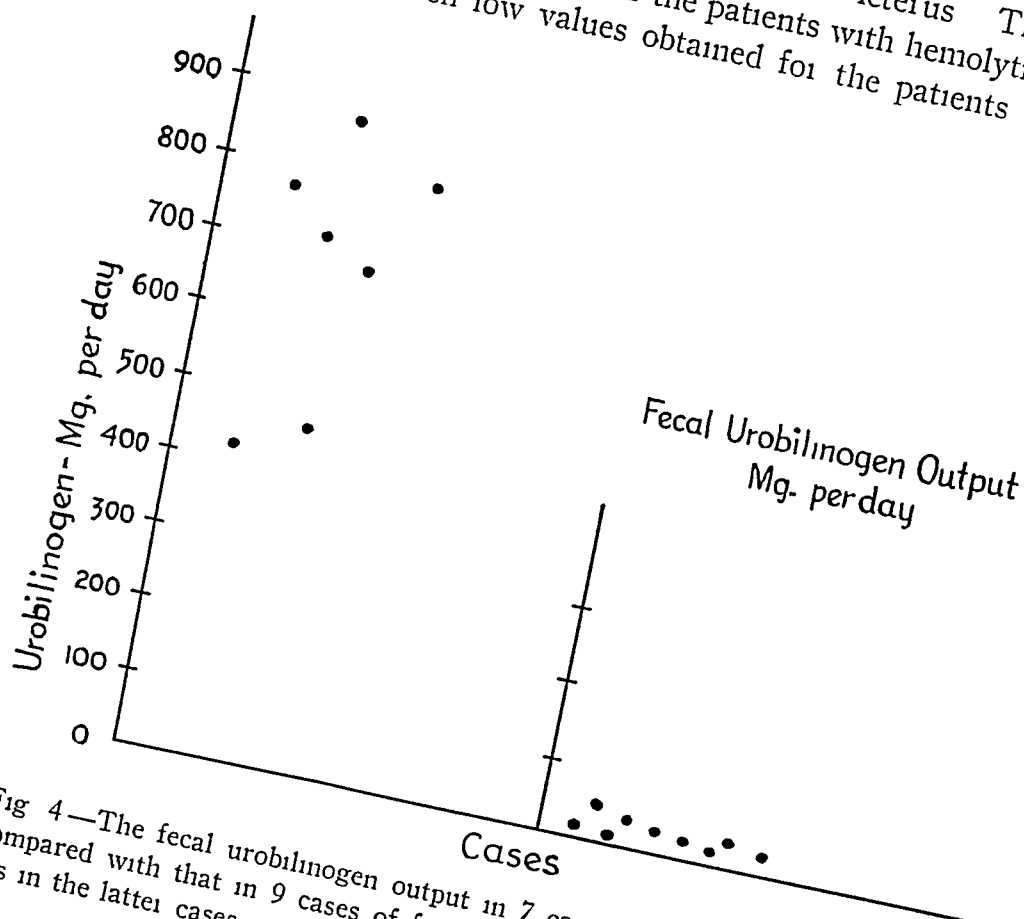


Fig 4—The fecal urobilinogen output in 7 cases of familial hemolytic icterus, as compared with that in 9 cases of familial nonhemolytic icterus. Note the low values in the latter cases, as compared with the high values in the former cases.

hemolytic jaundice is striking and serves to rule out all possibility of a hemolytic process, however mild, in the latter. We have recently demonstrated that the "bilirubin excretion test" may be of value in differentiating cases of mild jaundice of the two types. Thus, in the cases of nonhemolytic jaundice an abnormal type of curve was obtained which indicated delayed excretion of the bilirubin from the blood. Quite in contrast were the normal curves for excretion obtained in cases of mild hemolytic icterus with severe hemolytic icterus in the blood. (In the case of a patient with severe hemolytic icterus, however, with long-continued destruction of the blood and failure

of response to splenectomy, the bilirubin excretion from the blood was abnormal. This might indicate definite impairment in the function of the hepatic cells.)

The outstanding differential features of the two types are tabulated as follows:

Hemolytic Jaundice	Nonhemolytic Jaundice
Splenomegaly	Normal spleen
Spherocytosis	No spherocytosis
Abnormal thickness of the rouleaux	Normal thickness of the rouleaux
Increased fragility to sodium chloride	Normal fragility to sodium chloride
Increased fragility to lysolecithin	Normal fragility to lysolecithin
Reticulocytosis	Normal reticulocyte count
Increased content of urobilinogen in the urine	Normal content of urobilinogen in the urine
Greatly increased content of urobilinogen in the feces	Normal or low content of urobilinogen in the feces
Normal result of the bilirubin function test	Abnormal (delayed) result in the bilirubin function test

It should be noted that in a given case not all the features mentioned will necessarily be shown. The most constant and reliable are those of splenomegaly, spherocytosis as seen in rouleaux and in stained preparations, reticulocytosis and the amount of urobilinogen excreted in the feces.

B. Differentiation from Chronic Parenchymatous Disease of the Liver. The differentiation of nonhemolytic icterus and mild chronic disease of the liver (hepatitis, early cirrhosis) may be difficult and even impossible, especially in an isolated example of the former disease. Familial hepatitis is rare. Parsons²⁷ has recently reported cases of hepatitis in a family of 9 children, 4 of whom died of hepatic failure. The parents were not affected. Debré²⁸ has also reported cases of severe cirrhosis in children of several families. Wilson's disease (hepatolenticular degeneration) may perhaps be included under familial hepatitis. Familial disease does not necessarily signify hereditary disease, since the same toxic or infectious substance might have injured several members of the same family simultaneously. The occurrence of icterus in a family, particularly if at least two generations can be studied, as in the Ru family, serves to make unlikely the diagnosis of chronic progressive parenchymatous disease and to implicate a simple disturbance in function. However, it must be conceded that the separation of a "functional" abnormality and one due to slight "organic" disease is often difficult.

Chronic hepatitis, although in many cases subject to long remissions, sooner or later shows the evidences of progressive disease. In mild

27 Parsons, F. B. Familial Hepatitis, *Proc. Roy. Soc. Med.* **32**: 1197, 1939.

28 Debré, R. Familial Hepatitis and Chronic Jaundice, *Lancet* **1**: 760, 1939.

forms the blood bilirubin may be of the "indirect" variety,²⁹ and results of all the present day tests for liver function may be entirely normal. Features which may help to differentiate mild true hepatitis from the familial variety presented here are (1) the bilirubin in the urine and (2) the urobilinogen in the urine. However, the results of tests for these substances are subject to much variation and fluctuation. In a series of tests on the urine in a case of mild hepatitis, an occasional specimen may show the presence of bilirubin. Furthermore, the level of urobilinogen in the urine usually becomes increased early in the disease. When a diminished content of urobilinogen is present in the feces in association with hepatitis the stools are usually pasty or even clayey in color. In our familial groups of patients, however, even among those patients with low urobilinogen values, the stools were a normal brown.

In the cases of more severe hepatic disease, the spleen and liver may be enlarged, spider telangiectasias are often found, anemia, often of the macrocytic variety, may be present, "target" cells³⁰ and decreased fragility to sodium chloride or to lysolecithin may be present, there may be diminution in blood proteins and in cholesterol esters, the bilirubin is usually of the "direct" variety, and at least one of the several types of liver function tests yields an abnormal result.

Nature of Nonhemolytic Icterus and the Possible Pathologic Mechanisms Involved—Before discussing the possible pathologic mechanisms involved in this condition, it may be desirable to direct attention briefly to the normal physiologic processes involved in the formation and excretion of bilirubin.

The cycle of the conversion of the iron-containing pigment hemoglobin to the iron-free pigment bilirubin has been abundantly studied by numerous investigators.³¹ By a series of steps as yet poorly understood, iron is liberated from the hemoglobin of the red cells and the com-

29 That the blood bilirubin is of the "indirect" variety in the early stages or very mild forms of hepatitis, as in the early and convalescent stages of catarrhal jaundice, is not generally appreciated. The mildest disorders of the hepatic cells may not be associated with obstruction to the flow of bile and thus may not show "regurgitation" of "unlinked" bilirubin into the blood stream (Eppinger, H. *Leberkrankheiten*, Berlin, Julius Springer, 1937).

30 These are abnormally thin cells which in stained preparations resemble "bull's eyes" or targets. They are unusually resistant to hypotonic solutions of sodium chloride²⁴ and of lysolecithin.

31 Bingold, K. Ueber das Schicksal des überalterten Blutfarbstoffes im Organismus, *Ztschr f d ges exper Med* **99**:22, 1936. Lemberg, R. The Disintegration of Haemoglobin in the Animal Body, in *Perspectives in Biochemistry*, London, Cambridge University Press, 1938, p 137. Rich, A. R. The Formation of Bile Pigment, *Physiol Rev* **5** 182, 1925. Whipple, G. H. Pigment Metabolism and Regeneration of Hemoglobin in the Body, *Arch Int Med* **29** 711 (June) 1922.

pound bilirubin formed. According to Barron³² and others, bilirubin in the blood stream when first produced is bound to serum protein. This protein linkage is responsible for the "indirect" or "delayed" reaction with the van den Bergh test, since alcohol must be present to "unlink" the bilirubin from its protein combination. This "indirect" bilirubin then passes through the hepatic cells, during which passage an "unlinking" takes place so that the bilirubin then gives an "immediate" or

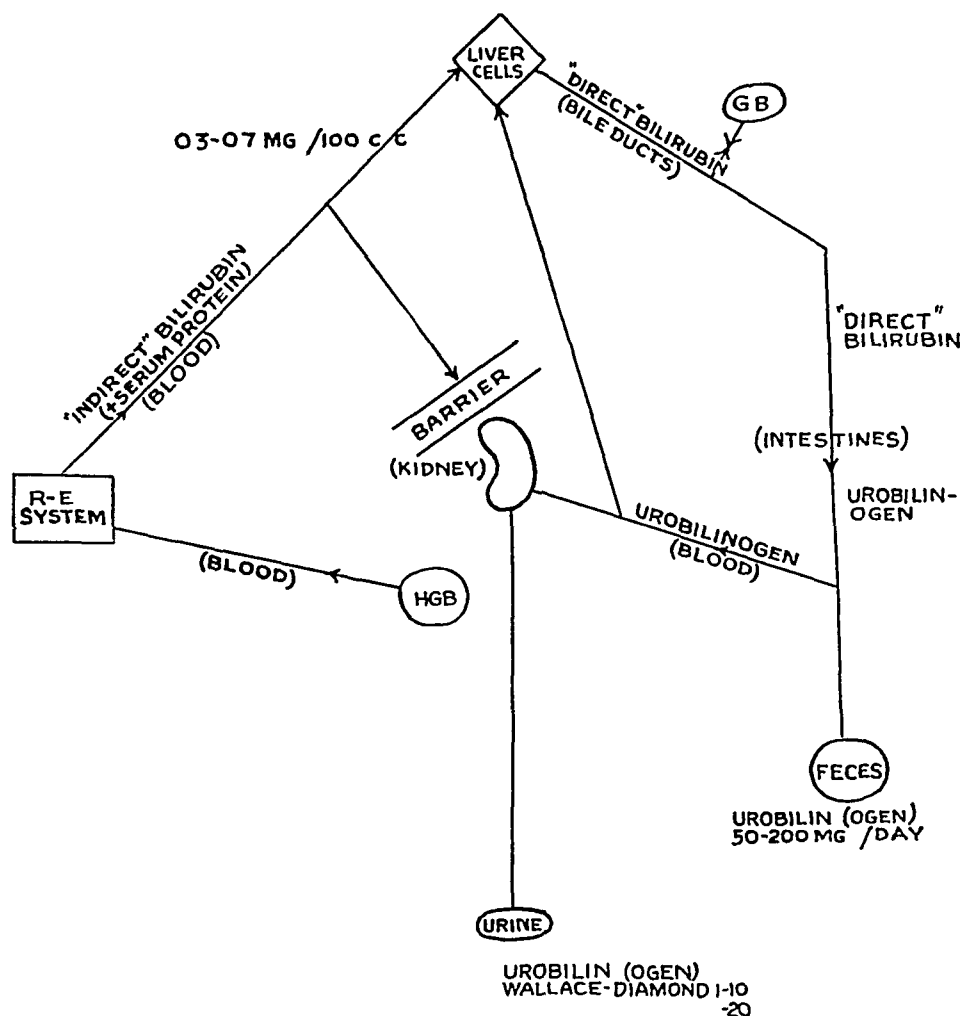


Fig 5—Diagrammatic representation of the normal bilirubin metabolism

"direct" reaction with the same van den Bergh test. Bilirubin is then excreted into the intestine, where it becomes converted into urobilinogen. Some of the latter material is reabsorbed by the intestinal mucosa into the blood stream and excreted by the kidneys into the urine.

Van den Bergh,³ in his discussion of cases of mild icterus, referred to otherwise healthy persons who had slightly increased values for blood

bilirubin. He concluded that they represented probable examples of physiologic hyperbilirubinemia. In other words, just as normal persons vary greatly in stature and a person of 76 inches (183 cm) is considered within the normal range, so it is conceivable that the normal content of bilirubin in the blood may range from 0.3 to 1.0 mg per hundred cubic centimeters. Some of Meulengracht's cases of the mildest form may have been instances of this type. Because the bilirubin values were usually well above 1.5 mg per hundred cubic centimeters in our patients, the possibility of simple physiologic bilirubinemia must be discarded.

Rich,³³ in his well known discussion of the pathogenesis of the forms of jaundice, mentioned four conditions under which jaundice may occur in the absence of obstruction: (1) when the threshold of the hepatic cells for bilirubin excretion is greatly raised, (2) when bilirubin is produced more rapidly than the hepatic cells can excrete it, (3) when the excretory mechanism is disturbed to such an extent that the bilirubin produced cannot be satisfactorily removed from the blood, or (4) when any combination of these factors occurs. To these conditions must be added a fifth, postulated by Bauer and Spiegel,³⁴ i. e., a "paracholic" icterus, in which bilirubin entering the endothelial spaces between the hepatic columns is rapidly reabsorbed into the blood before it can be taken up by the hepatic cells. Aschoff³⁵ induced such a condition experimentally by tying off the common bile duct. There was at first an increase in "indirect" bilirubin, due in all probability to regurgitation of "unlinked" bilirubin into the endothelial spaces and its subsequent appearance in the blood stream. Similar results were obtained by Lepehne.^{35a}

That icterus might be due to an increased threshold of the hepatic cells to excretion of bilirubin was not seriously considered by Rich, who stated that there was no evidence for its existence. Our studies led us to consider this as a possible factor in the pathogenesis in our cases of nonhemolytic icterus. The familial incidence of the condition, its benign nature and its persistence for many years without evidence of progressive hepatic impairment indicated a physiologic or "functional" disturbance rather than a disturbance due to well defined organic disease. A high threshold for the excretion of bilirubin from the blood might reasonably explain the disturbance, especially since this could conceivably

33 Rich, A. R. The Pathogenesis of the Forms of Jaundice, *Bull. Johns Hopkins Hosp.* **47**: 338, 1930.

34 Bauer, J., and Spiegel, A. Ueber das Bilirubin im Blute und seine pharmakologische Beeinflussbarkeit, *Deutsches Arch. f. klin. Med.* **129**: 17, 1919.

35 Aschoff, L., cited by Eppinger, H. *Leberkrankheiten*, Berlin, Julius Springer, 1937.

35a Lepehne, G. Experimentelle Untersuchungen in mechanischen und dynamischen Icterus, *Deutsches Arch. f. klin. Med.* **136**: 88, 1921.

be inherited. Against this possibility was placed the reaction to injected bilirubin. If the "threshold" were fixed, say at 2 mg per hundred cubic centimeters, the injection of an amount of bilirubin sufficient to raise the bilirubin content of the blood to 4 mg should be followed by a quick drop in bilirubin to the original value of 2 mg. This did not occur in our cases, in which excretion of bilirubin from the blood stream after intravenous injection of the material was definitely delayed. This delay indicated that the passage of bilirubin through the hepatic cells was retarded and, in the absence of other evidences of disturbed function of the liver, pointed to a selective abnormality in bilirubin excretion by the hepatic cells (retention jaundice).

We believe that the evidence now at hand in our cases points to the presence of a "constitutional hepatic dysfunction" in which the permeability of the hepatic cells to the passage of bilirubin is probably disturbed, with resultant "regurgitation" of this substance first into the endothelial spaces of the liver and thence into the blood stream. In this type of "regurgitant" jaundice, in contrast to that described by Rich, the bilirubin is of the "indirect" type, since it has not passed through the liver cells but is simply retained longer than usual in the blood stream. Histologic examination of liver tissue in our cases was not possible, although Meulengracht (personal communication) stated that he performed a puncture biopsy of the liver in 1 of his cases, with completely negative results.

Toward the close of the present study, we learned of the results of an investigation by Malloy and Lowenstein³⁶ on a strain of rats which showed hereditary jaundice. The analogies between these families of jaundiced rats and our own human families are striking. Gunn described the mendelian recessive character of jaundice in a mutant strain of Wistar albino rats and suggested the analogy with hemolytic jaundice in human beings. Malloy and Lowenstein found no direct evidence from the blood picture, fragility tests, bone marrow or urobilinogen excretion that the jaundice was primarily of hemolytic origin, although the serum bilirubin was invariably of the indirect type, which is usually considered indicative of hemolytic jaundice.

Their experiments indicated that "the bilirubinemia was due to the inability of the liver to transform indirect to direct bilirubin at a rate sufficient for normal excretion." Indirect bilirubin injected intravenously into jaundiced rats was unchanged in the blood, which demonstrated impairment of excretion in the jaundiced rats. The amount of urobilin excreted in the stool was less than normal, but not entirely absent. Results of other liver function tests, namely, the bromsulphalein and

36 Malloy, H. T., and Lowenstein, L. Hereditary Jaundice in Rat, *Canad M. A. J.* 42: 122, 1940.

Takata-A1a tests and determination of plasma prothrombin levels, were normal in the jaundiced rats. Histologic examination of the liver revealed no morphologic abnormality. It was concluded that the jaundiced rats had retention jaundice caused by the inability of the liver to make direct bilirubin at a rate sufficient for normal excretion.

It appears likely that the hereditary jaundice of rats as described by Malloy and Lowenstein and familial nonhemolytic icterus as described in this paper are similar disorders. It is of interest that the same general conclusions regarding such questions as pathogenesis were independently arrived at in both the investigations on human beings and in those on rats and that histologic examination of the liver in the jaundiced rats failed to reveal any morphologic abnormality. This may indicate a simple disturbance in the function of the liver relating to the excretion of "indirect" bilirubin.

SUMMARY

Two families with an unusual type of chronic hereditary jaundice were studied. Although the bilirubin was of the "indirect" variety, thus suggesting a hemolytic process, the absence of splenomegaly, spherocytosis, reticulocytosis, increased fragility to sodium chloride and lysolecithin and hyperactivity of the bone marrow contraindicated the diagnosis of familial hemolytic icterus. The latter disease was, furthermore, conclusively ruled out by the normal or even somewhat low values for daily urobilinogen output in the feces. The hereditary nature of the disorder and its long duration without symptoms or signs of progressive hepatic disease indicated a simple disturbance in the function of the liver. A significant abnormality was the greatly delayed excretion of injected bilirubin from the blood, indicating (in absence of other evidences of disturbed function of the liver) an alteration in the permeability of the hepatic cells which retarded the excretion of bilirubin. Striking analogies were present between the familial nonhemolytic jaundice in human beings in our cases and the hereditary jaundice of rats described by Malloy and Lowenstein, both conditions may represent a "constitutional hepatic dysfunction" (Rozendaal, Comfort and Snell). Our studies have further demonstrated that familial jaundice is not always hemolytic in type and that an indirect van den Bergh reaction is not necessarily indicative of a hemolytic process.

NOTE—Since this paper was submitted, another family has been observed. Splenectomy had been suggested for one of the persons in this family because the diagnosis of familial hemolytic jaundice had been made. In addition, 4 young persons with the symptoms, signs and laboratory phenomena in the cases described in this paper were studied, unfortunately, studies of the families of these 4 persons could not be made.

PNEUMOCOCCIC PNEUMONIA

AN ANALYSIS OF THE RECORDS OF 1,469 PATIENTS TREATED IN
THE LOS ANGELES COUNTY HOSPITAL FROM
1934 TO 1938 INCLUSIVE

III TYPE SPECIFIC ANTIPNEUMOCOCCUS SERUM THERAPY QUANTITATIVE RELATIONS BETWEEN DOSAGE AND RESULTS

FREDERICK J MOORE, B A

ROY E THOMAS, M D

BURRELL O RAULSTON, M D

ANSON HOYT, M D

AND

JOHN D WALTERS, B A

LOS ANGELES

Treatment of pneumococcic pneumonia with type-specific antipneumococcus serum has received wide attention¹ "Adequate" treatment is said to hasten recovery and improve the outcome Three major

This study was aided by the Pneumonia Fund of the School of Medicine, University of Southern California

From the Department of Medicine, School of Medicine, University of Southern California and from the Los Angeles County Hospital

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(Footnote continued on next page)

factors determine the "adequacy" of serum the duration of the untreated disease, the total amount of serum given and the rapidity of

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MATERIALS AND METHODS²

In the preceding articles³ certain data have been presented concerning all (1,469) patients with typed pneumococcic pneumonia treated in the Los Angeles County Hospital during the five year period 1934 to 1938. Of these, 569 received specific serum therapy, but 56 cases were discarded because the records were inadequate. The remaining 513 are otherwise unselected.

All patients received commercial type-specific, horse or rabbit antipneumococcus serum intravenously, in various hospital services, at the order of many different physicians and in widely varying dosage.

The entire clinical, nursing and laboratory record of each patient was abstracted in detail by some of the group of workers. The abstracts were checked by one of us with the original records, and the data were then analyzed⁴ to determine the relation of treatment to outcome and to the defervescence. Certain terms, illustrated in figure 1, have been used throughout this paper.

In studying the relation of treatment to outcome, we used the following terms: U is the total number of thousand units of serum received by the patient, H is the number of hours between the first and the last dose of serum (with a minimum

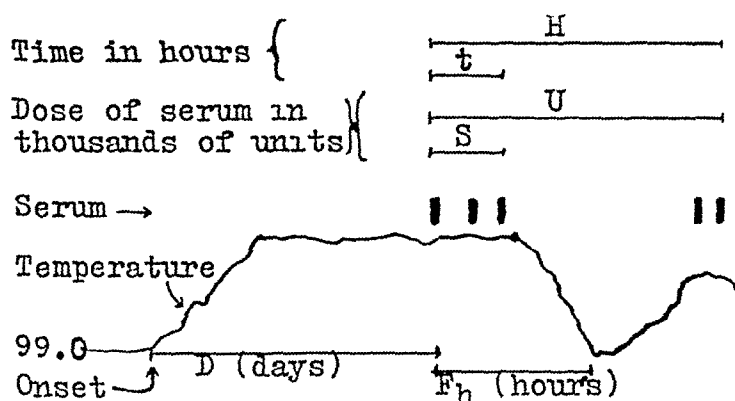


Fig 1—Explanation of symbols

of 1) and D is the number of days from the onset (first appearance of chill, fever, painful respiration, bloody sputum, dyspnea or prostration) of pneumonia to the first dose of serum (with a minimum of 1). The relation of treatment to outcome was studied in all (513) patients.

The relation of treatment to the defervescence was studied in the 462 patients whose temperature after serum therapy fell to 99.0 F or less before cure, death or recognition of a complication. The following terms have been used: S is the

² Dr Thurston H. Ross, of the School of Merchandizing, University of Southern California, has "examined the statistical method developed in this paper, and found that, though unique, it is adequate to support the findings indicated."

³ Moore, F. J., and others. *Pneumococcic Pneumonia. An Analysis of the Records of 1,469 Patients Treated in the Los Angeles County Hospital from 1934 to 1938, Inclusive*, I Character of Pneumonia Caused by the Various Types, Complications of Pneumonia, Outcome of Pneumonia in the Presence of Certain Variations in the Patient and in the Course of the Disease, *Arch Int Med* **66** 1290-1316 (Dec.) 1940, II Outcome and Character of Pneumonia in the Presence of Associated or Concomitant Disease, *ibid* **66** 1317-1330 (Dec.) 1940.

⁴ Mary Cunliffe Moore and Josephine Abraham aided in the conduct of the analysis.

amount of serum, in thousands of units, given before the first normal temperature reading (99.0 F or less), while *t* is the time in hours from the first to the last dose of serum given before the first normal temperature reading (minimum of 1), *F_h* is the number of continuously febrile hours following the first dose of serum, *e g*, the number of hours from the first dose to the first normal temperature reading—it implies nothing about the occurrence of subsequent fever. The character of the defervescence (crisis or lysis) and the recurrence of fever (over 99.0 F) have also been noted.

The outcome has been recorded as "optimum outcome"⁵ (survival without complication), "dead" (accidental deaths have been excluded from this study) or "complicated" (as defined in paper I).

Certain aspects of our findings have been found to be more readily understood if their presentation is preceded by an outline of the preliminary findings and the subsequent analysis.

TABLE 1—*Outcomes Attending Variations in U (total dose in thousands of units), D (number of days from onset to first dose) and H (number of hours from first to last dose)*

Table 1a					Table 1b					Table 1c				
% Outcome					% Outcome					% Outcome				
U	Pt*	oo†	d‡	c§	D	Pt	oo	d	c	H	Pt	oo	d	c
1-20	15	60	33	7	1	27	96	0	4	1-2	37	70	22	11
21-40	25	70	26	9	2	72	85	3	14	3-4	42	74	17	12
41-60	35	74	25	9	3	75	85	7	12	5-6	40	88	3	12
61-80	33	70	15	21	4	82	71	17	15	7-8	60	85	7	8
81-100	108	79	11	11	5	81	68	19	17	9-10	41	81	17	7
101-120	32	75	9	19	6	57	70	18	18	11-14	49	69	22	16
121-140	63	81	2	17	7	42	48	33	31	15-20	60	73	15	15
141-160	31	84	13	6	8	44	59	27	18	21-30	69	74	13	15
161-180	36	72	6	28	9-11	19	37	37	47	31-50	60	47	23	37
181-200	23	65	13	26	12-31	18	56	33	22	51-100	46	67	22	22
201-220	23	65	22	22						101 & up	21	38	38	48
221-260	31	58	32	16										
261-300	23	61	26	17										
301-400	22	45	32	41										
401 & up	17	41	47	35										

* Number of patients † Optimum outcome ‡ Dead § Complicated

We examined the outcome attending various total dosages (*U*), expecting to find an improving outcome with increasing dosage. This relation was found (table 1a) only with relatively small amounts of serum, larger amounts being accompanied by an increasingly poor outcome. The anomaly was thought to have been due to either or both of the following facts: (1) Patients receiving the larger doses of serum had much greater need for serum than did those receiving smaller doses, (2) the larger amounts were spread out over such a long period of time that they were ineffective.

The need for serum is well known to increase with the duration of the disease untreated. We found (table 1b) that the outcome was definitely impaired with increasing numbers of days (*D*) from the onset to the first dose of serum, the dosage not being considered. It was apparent that *D* might be used as an index.

5 Since a patient may die with a complication and hence appear under both headings, there is need of the optimum outcome rate, for it permits calculation of the degree of overlap between the death and complication rates. The sum of the three rates minus 100 equals the degree of overlap. The optimum outcome rate is of great interest per se.

of the need for serum or that division of the total dose by D might give a quotient any value of which was accompanied by a constant outcome (regardless, that is, of the actual value of either U or D)

The number of hours (H) between the first and the last dose of serum was also examined, the expectancy being that the outcome was increasingly poor with increasing values of H. As seen in table 1c, this was actually found except for very small values of H. This intimated that the rate of serum administration, or U/H, should be considered rather than the total dose alone. When U/H was substituted for U, the expression U/D, previously noted, became U/HD, or the amount of serum per hour per day untreated.

When U/HD was studied in a similar manner, it presented a fairly satisfactory correlation with outcome. However, if the patients were divided according to D (days untreated), it was found that patients with similar U/HD but different D values differed considerably in outcome. The criterion that a given value of the expression should be accompanied by a given outcome regardless of the actual value of U, H or D was therefore not met. Certain other expressions were hence examined: U/HD^2 , U^2/HD^3 , U/HD^3 , and similar expressions omitting H. The correlation of U/HD^3 with the outcome was more acceptable than that of the other formulas, and it is presented alone. Since the relation was logarithmic, we have dealt with the logarithm of the expression rather than its numerical value.⁶

To be acceptable, it was also expected that the general form of the relation between U/HD^3 and the outcome should be independent of bacteremia, pulmonary involvement and other factors that may alter the effectiveness of serum. It was not expected that the same outcome should attend the same treatment under those various conditions, but only that parallel alterations in outcome should be found with alterations in U/HD^3 . Several factors were examined in this manner.

With regard to the effect of serum on the temperature, an attempt was made to discover a relation between treatment preceding the defervescence and the interval of time between the beginning of treatment and the first normal temperature. The amount of serum per hour, S/t (S being the number of thousand units given before the first normal temperature and t the time in hours between the first and last injection), was plotted against the number of hours the patient was continuously febrile, F_h (the number of hours between the first dose of serum and the first normal temperature reading). The correlation was found adequate, and other formulas were not considered. The relation was examined to determine whether it could have been due solely to S, to the extent of pulmonary involvement or to the incidence of bacteremia. It was more closely examined to determine the effect of the number of days untreated (D) and of those types represented by sufficient numbers to warrant study (I, II, VII, the remainder being pooled).

FINDINGS

Relations Between Dosage and Outcome—The data showing the relation of U/HD^3 to outcome are presented numerically in table 2, parts 1 to 12, while mean percentages (calculated by the method of least squares) are indicated in graphs (fig. 2) corresponding to the parts of the table.

⁶ When the \log_{10} of $U/H \cdot D^3$ equaled zero, the patient received 1,000 units of serum per hour for the cube of the number of days untreated. This obviously implies nothing about the actual value of U, H or D—which is the reason the formula must be proved valid regardless of the actual value of U, H or D.

TABLE 2—*Relation Between Outcome and U/HD³, in All (513) Scurm-Treated Patients*

The table is composed of twelve parts, each of which gives numerical data and corresponds to a graph giving the data in percentage form (mean per cents, calculated by the method of least squares) Part 1 indicates outcome of all patients grouped according to class intervals of 0.3 mean log U/HD³, and the actual values of U/HD³, the remainder of the table indicates the effect of certain other variables U, total dose in thousands of units H, number of hours between first and last dose (minimum of 1), D, number of days from onset to first dose (minimum of 1), 00, optimum outcome, d, dead, c, complicated Tl, total number of patients

Part 1—All Patients								
Mean Log U/HD ³	Actual Numerical Values of U/HD ³				Tl	oo	d	c
—3 6667	0 0002 to 0 0003				2	0	2	0
—3 3333	0 0004 to 0 0007				1	0	1	1
—3 0000	0 0008 to 0 0015				6	4	1	2
—2 6667	0 0016 to 0 0032				7	3	2	2
—2 3333	0 0033 to 0 0068				17	7	4	9
—2 0000	0 0069 to 0 0147				31	17	9	8
—1 6667	0 0148 to 0 0316				74	44	18	18
—1 3333	0 0317 to 0 0681				86	57	22	10
—1 0000	0 0682 to 0 1468				79	54	12	18
—0 6667	0 1469 to 0 3161				55	40	11	7
—0 3333	0 3162 to 0 6813				60	54	2	5
0 0000	0 6814 to 1 4680				39	31	1	8
0 3333	1 4681 to 3 1610				26	23	0	3
1 2856	3 1611 to 200 00				30	30	0	0
Total					510	364	85	89

Part 2a—U, or Total Dose in Thousands of Units																
Mean Log U/HD ³	U 1 to 80				U 81 to 120				U 121 to 200				U 201 and Over			
	Tl	oo	d	c	Tl	oo	d	c	Tl	oo	d	c	Tl	oo	d	c
—3 67	0				1	0	1	0	0				1	0	1	0
—3 33	0				0				0				1	0	1	1
—3 00	1	1	0	0	3	1	1	2	0				2	2	0	0
—2 67	0				2	1	1	0	4	2	0	2	1	0	1	0
—2 33	3	2	1	1	4	1	1	2	7	2	1	5	3	2	1	1
—2 00	9	4	3	3	7	4	2	1	6	5	0	1	9	4	4	3
—1 67	12	7	4	1	20	13	6	1	23	16	1	7	19	8	7	9
—1 33	23	13	7	3	16	15	0	1	20	15	3	2	28	14	12	4
—1 00	17	12	3	3	18	14	2	3	24	16	4	6	20	12	3	6
—0 67	15	10	5	1	17	16	0	1	11	8	1	2	12	6	5	1
—0 33	13	12	1	1	18	16	1	1	17	17	0	0	12	9	0	3
0 00	5	5	0	0	15	12	0	3	17	13	0	4	2	1	1	1
0 33	6	5	0	1	7	5	0	2	10	10	0	0	3	3	0	0
1 29	3	3	0	0	11	11	0	0	13	13	0	0	3	3	0	0
Total	106	74	24	14	139	109	15	17	152	117	10	29	116	64	36	29

Part 2b—H, or Number of Hours Between First and Last Dose																
Mean Log U/HD ³	H 1 to 6				H 7 to 14				H 15 to 30				H 31 and Over			
	Tl	oo	d	c	Tl	oo	d	c	Tl	oo	d	c	Tl	oo	d	c
—3 67	0				1	0	1	0	0				1	0	1	0
—3 33	0				0				0				1	0	1	1
—3 00	0				1	0	1	1	2	2	0	0	3	2	0	1
—2 67	0				0				2	1	1	0	5	2	1	2
—2 33	0				4	2	2	1	4	3	0	1	9	2	2	7
—2 00	4	1	1	2	3	2	1	0	8	4	3	1	16	10	4	5
—1 67	3	2	1	0	17	9	6	2	24	16	4	5	30	17	7	11
—1 33	14	9	4	1	24	19	5	2	23	16	4	3	25	13	9	4
—1 00	16	12	3	3	24	19	2	3	23	16	5	4	16	7	2	8
—0 67	15	10	4	1	24	19	3	3	8	7	0	1	8	4	4	0
—0 33	14	13	1	1	25	22	1	2	13	13	0	0	8	6	0	2
—0 00	15	13	0	2	11	10	0	1	12	8	0	4	1	0	1	1
0 33	11	9	0	2	9	9	0	0	2	2	0	0	4	3	0	1
1 29	16	16	0	0	6	6	0	0	7	7	0	0	1	1	0	0
Total	108	85	14	12	149	117	22	15	128	95	17	19	128	67	32	43

TABLE 2—*Relation Between Outcome and U/HD³, in All (513) Serum-Treated Patients—Continued*

Mean Log U/HD ³	Part 2c—D, or Number of Days from Onset to First Dose											
	D 1 to 3				D 4 to 6				D 7 and Over			
	Tl	oo	d	e	Tl	oo	d	e	Tl	oo	d	e
—3.67	0				0				2	0	2	0
—3.33	0				0				1	0	1	1
—3.00	0				0				6	4	1	2
—2.67	0				0				7	3	2	2
—2.33	0				2	1	1	1	15	6	5	8
—2.00	0				11	8	2	1	20	9	7	7
—1.67	0				39	25	7	9	35	19	11	9
—1.33	3	3	0	0	54	36	13	7	29	18	9	3
—1.00	13	6	2	7	58	44	7	9	8	4	3	2
—0.67	21	18	3	1	34	22	8	4	0			
—0.33	43	39	1	3	17	15	1	2	0			
0.00	35	29	1	6	4	2	0	2	0			
0.33	26	23	0	3	0				0			
1.29	30	30	0	0	0				0			
Total	171	148	7	20	219	153	39	35	123	63	39	34

Log U/HD ³	Part 3—Type of Pneumococcus											
	Type I				Type II				Type III			
	Tl	oo	d	e	Tl	oo	d	e	Tl	oo	d	e
—3.67	1	0	1	0	0				1	0	1	0
—3.33	1	0	1	1	0				0			
—3.00	3	1	1	2	1	1	0	0	2	2	0	0
—2.67	5	2	1	2	2	1	1	0	0			
—2.33	8	3	1	5	3	1	1	2	2	2	0	0
—2.00	12	7	3	3	2	1	0	1	7	5	0	2
—1.67	33	23	5	8	7	4	2	1	18	10	5	5
—1.33	33	26	4	4	10	7	2	2	28	16	11	2
—1.00	41	28	5	11	5	4	1	1	15	10	2	3
—0.67	25	22	2	2	5	1	3	1	12	7	3	2
—0.33	25	23	0	2	10	9	1	1	10	10	0	0
0.00	17	14	0	3	5	3	1	2	4	4	0	0
0.33	9	9	0	0	3	1	0	2	6	6	0	0
1.29	11	11	0	0	5	5	0	0	5	5	0	0
Total	224	169	24	43	58	38	12	13	110	77	22	14

Mean Log U/HD ³	Part 4—Results of Blood Culture in 142 Patients							
	1 or More Positive				All Cultures Negative			
	Tl	oo	d	e	Tl	oo	d	e
—3.67	0				0			
—3.33	1	0	1	1	0			
—3.00	0				2	1	1	1
—2.67	0				1	1	0	0
—2.33	0				7	3	2	4
—2.00	2	0	2	1	7	5	1	2
—1.67	1	1	0	0	18	7	7	7
—1.33	1	0	1	0	20	11	7	3
—1.00	3	2	0	1	25	18	5	5
—0.67	2	0	2	0	11	9	1	1
—0.33	1	1	0	0	22	18	4	0
0.00	1	0	1	1	6	4	0	2
0.33	0				4	3	0	1
1.29	1	1	0	0	6	6	0	0
Total	13	5	7	4	129	86	28	26

Mean Log U/HD ³	Part 5—Pulmonary Involvement "Lobar" Includes Clinically Lobar Lesions Found at Autopsy to be Atypical											
	Typically Lobar (Clinical Diagnosis)											
	1 Lobe				2 Lobes				3 to 5 Lobes			
	Tl	oo	d	e	Tl	oo	d	e	Tl	oo	d	e
—3.67	0				1	0	1	0	1	0	1	0
—3.33	1	0	1	1	0				0			
—3.00	2	1	0	1	1	1	0	0	2	1	1	1
—2.67	2	1	0	1	3	1	1	1	2	1	1	0
—2.33	8	5	1	3	2	1	0	1	5	0	2	5
—2.00	13	7	5	1	11	7	2	3	4	1	2	3
—1.67	40	29	4	8	23	13	6	6	9	1	7	4
—1.33	50	39	8	5	16	8	6	3	13	6	6	1
—1.00	50	40	2	9	13	8	1	4	10	4	6	3
—0.67	37	31	4	3	12	8	3	2	2	1	1	0
—0.33	41	38	1	2	10	7	1	3	6	6	0	0
0.00	31	26	1	5	5	2	0	3	0			
0.33	21	20	0	1	4	2	0	2	0			
1.29	25	25	0	0	2	2	0	0	0			
Total	321	261	27	40	103	60	21	28	54	21	27	17

Mean Log U/HD ³	Distinctly Atypical							
	Tl	oo	d	e	Tl	oo	d	e
	Tl	oo	d	e	Tl	oo	d	e
—3.67	0				0			
—3.33	1				0			
—3.00	1	1	0	0	1	1	0	0
—2.67	0				0			
—2.33	2	1	1	0	2	1	1	0
—2.00	3	1	1	0	3	1	1	0
—1.67	2	1	1	0	2	1	1	0
—1.33	7	4	2	1	7	4	2	1
—1.00	6	2	3	2	6	2	3	2
—0.67	4	1	3	0	4	1	3	0
—0.33	3	3	0	0	3	3	0	0
0.00	3	3	0	0	3	3	0	0
0.33	1	1	0	0	1	1	0	0
1.29	3	3	0	0	3	3	0	0
Total	35	22	10	4	35	22	10	4

TABLE 2—*Relation Between Outcome and U/HD³, in All (513) Serum-Treated Patients—Continued*

Part 6—Maximum Reported Total Leukocyte Count in Thousands of Cells (360 Patients)												
Mean Log U/HD ³	0 to 9				10 to 29				30 and Over			
	Tl	oo	d	c	Tl	oo	d	c	Tl	oo	d	c
-3.67	0				1	0	1	0	0			
-3.33	0				1	0	1	1	0			
-3.00	0				3	3	0	0	1	0	1	1
-2.67	1	1	0	0	4	1	2	1	2	1	0	1
-2.33	1	0	1	1	11	5	2	5	2	1	0	1
-2.00	2	1	0	1	16	9	5	3	5	3	2	1
-1.67	2	1	1	0	39	24	6	11	7	4	2	1
-1.33	9	5	3	2	49	36	9	4	5	3	2	1
-1.00	7	5	1	2	45	30	6	11	6	5	0	1
-0.67	4	2	2	0	27	21	4	3	2	2	0	0
-0.33	10	9	0	1	26	25	0	1	5	4	0	1
0.00	3	3	0	0	22	16	1	6	7	5	0	2
0.33	4	4	0	0	12	9	0	3	3	3	0	0
1.29	4	4	0	0	11	11	0	0	1	1	0	0
Total	47	35	8	7	267	190	37	49	46	32	7	10

Part 7—Season												
Mean Log U/HD ³	Winter Dec to Feb				Spring March and April				Summer May to Sept			
	Tl	oo	d	c	Tl	oo	d	c	Tl	oo	d	c
-3.67	2	0	2	0	0				0			
-3.33	0				0				1	0	1	1
-3.00	3	1	1	2	0				3	3	0	0
-2.67	5	2	1	2	1	0	1	0	1	1	0	0
-2.33	10	3	3	6	3	1	1	2	1	0	0	1
-2.00	11	4	4	4	7	3	3	2	5	5	0	0
-1.67	44	29	10	8	10	3	4	4	11	6	1	4
-1.33	37	21	11	6	12	7	3	3	23	19	4	1
-1.00	32	23	4	7	20	12	5	5	14	10	1	4
-0.67	26	19	6	1	7	6	0	1	16	12	2	2
-0.33	26	24	1	1	16	15	1	1	10	8	0	2
0.00	10	9	0	1	9	8	0	1	13	10	0	3
0.33	10	8	0	2	9	9	0	0	4	3	0	1
1.29	18	18	0	0	4	4	0	0	5	5	0	0
Total	244	161	47	40	98	68	18	19	107	82	9	19

Part 8—Age												
Mean Log U/HD ³	0 to 19				20 to 39				40 to 59			
	Tl	oo	d	c	Tl	oo	d	c	Tl	oo	d	c
-3.67	0				0				1	0	1	0
-3.33	0				0				1	0	1	1
-3.00	1	1	0	0	0				4	3	0	1
-2.67	0				4	2	0	2	3	1	2	0
-2.33	1	0	1	1	10	4	1	6	3	1	1	2
-2.00	4	2	0	2	14	8	3	4	10	5	5	2
-1.67	6	3	1	2	33	22	6	5	27	16	6	9
-1.33	7	6	1	0	42	30	7	6	28	16	10	3
-1.00	8	5	0	3	36	28	3	5	24	17	3	7
-0.67	11	11	0	0	27	21	4	3	12	6	4	2
-0.33	11	10	0	1	25	24	0	1	19	16	1	3
0.00	10	8	0	2	21	16	1	5	6	5	0	1
0.33	3	3	0	0	12	10	0	2	10	9	0	1
1.29	6	6	0	0	18	18	0	0	4	4	0	0
Total	68	55	3	11	242	183	25	39	152	99	34	32

Part 9—Race												
Mean Log U/HD ³	Caucasian				Other Races							
	Tl	oo	d	c	Tl	oo	d	c				
-3.67	1	0	1	0	1	0	1	0				
-3.33	1	0	1	1	0							
-3.00	3	2	1	1	3	2	0					
-2.67	5	2	1	2	2	1	1	0				
-2.33	15	7	3	7	2	0	1	2				
-2.00	19	8	8	6	12	9	1	2				
-1.67	57	38	10	11	17	6	8	7				
-1.33	57	36	15	8	29	21	7	2				
-1.00	64	43	10	15	15	11	2	3				
-0.67	41	30	8	4	14	10	3	1				
-0.33	49	47	0	2	11	7	2	3				
0.00	29	22	0	7	10	9	1	1				
0.33	18	15	0	3	8	8	0	0				
1.29	22	22	0	0	8	8	0	0				
Total	381	272	58	67	132	92	27	22				

TABLE 2—*Relation Between Outcome and U/HD³, in All (513) Serum-Treated Patients—Continued*

Part 10—Sex								
Mean Log U/HD ³	Male				Female			
	Tl	oo	d	c	Tl	oo	d	c
—3.67	1	0	1	0	1	0	1	0
—3.33	1	0	1	1	0			
—3.00	3	2	1	1	3	2	0	1
—2.67	6	2	2	2	1	1	0	0
—2.33	9	2	3	6	8	5	1	3
—2.00	22	11	7	7	9	6	2	1
—1.67	52	29	14	14	22	15	4	4
—1.33	59	40	15	7	27	17	7	3
—1.00	58	41	10	12	21	13	2	6
—0.67	38	26	9	4	17	14	2	1
—0.33	36	33	2	2	24	21	0	3
0.00	26	21	1	5	13	10	0	3
0.33	16	15	0	1	10	8	0	2
1.29	22	22	0	0	8	8	0	0
Total	349	244	66	62	162	120	19	27

Part 11—Maximum Temperature During First Few Hours of Hospitalization												
Mean Log U/HD ³	99 to 101				102 and 103				104 and Over			
	Tl	oo	d	c	Tl	oo	d	c	Tl	oo	d	c
—3.67	0				2	0	2	0	0			
—3.33	0				1	0	1	1	0			
—3.00	2	2	0	0	2	1	1	1	2	1	0	0
—2.67	1	1	0	0	3	1	1	1	3	1	1	1
—2.33	1	0	1	0	8	3	1	5	8	4	2	4
—2.00	7		2	0	12	6	3	5	11	6	4	3
—1.67	15	9	9	1	38	23	8	11	21	12	5	6
—1.33	14	6	8	1	49	38	8	5	23	13	6	4
—1.00	9	5	4	2	45	33	5	10	25	16	3	6
—0.67	4	4	0	0	33	20	9	5	18	16	2	0
—0.33	3	3	0	0	22	17	2	4	35	34	0	1
0.00	0				23	19	1	4	16	12	0	4
0.33	3	2	0	1	13	12	0	1	10	9	0	1
1.29	2	2	0	0	18	18	0	0	10	10	0	0
Total	61	39	20	5	269	191	42	53	183	134	23	31

Part 12—Concomitant Conditions								
Mean Log U/HD ³	Not Recorded ("Absent")				Known to be Present			
	Tl	oo	d	c	Tl	oo	d	c
—3.67	2	0	2	0	0			
—3.33	0				1	0	1	1
—3.00	3	2	1	1	3	2	0	1
—2.67	7	3	2	2	0			
—2.33	9	4	2	5	8	3	2	4
—2.00	19	11	3	6	12	6	6	2
—1.67	37	25	5	10	37	19	13	8
—1.33	45	33	10	2	41	24	12	8
—1.00	39	27	5	10	40	27	7	8
—0.67	29	24	2	3	26	16	9	2
—0.33	35	30	1	5	25	24	1	0
0.00	18	15	0	3	21	16	1	5
0.33	13	10	0	3	13	13	0	0
1.29	18	18	0	0	12	12	0	0
Total	274	202	33	50	259	162	52	39

Table 2, part 1, and figure 2, graph 1, indicate that the outcome was a function ⁷ of the amount of serum per hour per day (cubed) untreated. In general, the percentage outcome equaled $a + b (\log_{10} U/HD^3)$, in which formula a and b are constants for each index of

⁷ A variable y is said to be a function of a variable x if there exists a law whereby, when x is given, y is determined. The fact that a definite relation exists is of the first importance, the general statement of the law is less important, the numerical values obtained are relatively inconsequential.

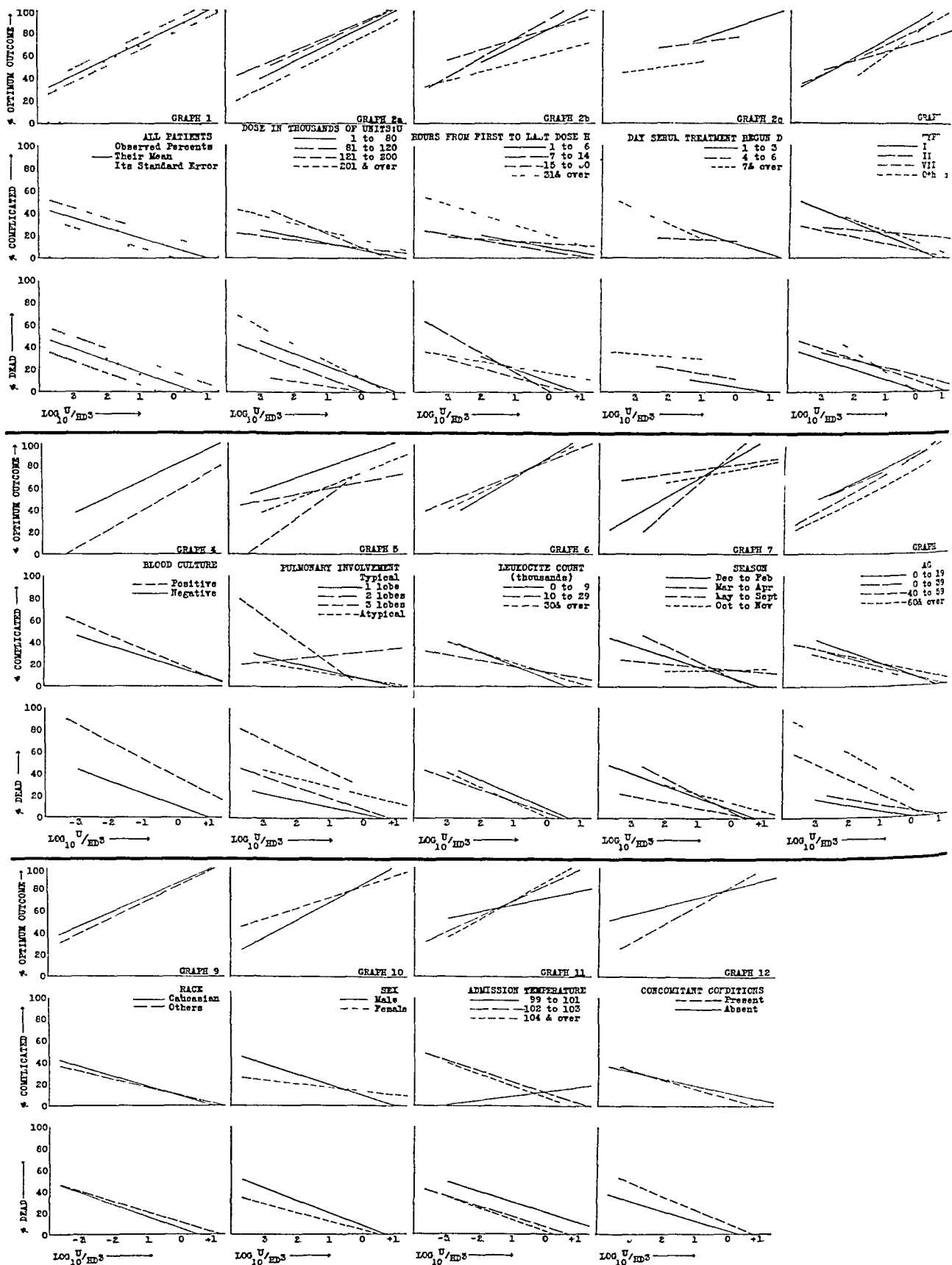


Fig 2—Relation between outcome and U/HD^3 , in all (513) serum-treated patients. Each of the twelve graphs presents, in percentage form, numerical data from the correspondingly numbered part of table 2.

outcome, U is the total dose of serum in thousands of units, H is the number of hours between the first and the last dose of serum and D is the number of days from the onset of pneumonia to the first dose of serum (days the patient was untreated). The following are the equations drawn in figure 2, graph 1, the standard errors being indicated by plus or minus variations about a

- (1) % Optimum Outcome = $(84.7 \pm 5.8) + 14.86 (\log_{10} U/HD^3)$,
- (2) % Complicated = $(9.1 \pm 9.0) - 8.98 (\log_{10} U/HD^3)$, and
- (3) % Dead = $(6.7 \pm 11.3) - 10.67 (\log_{10} U/HD^3)$

As outlined above, it is necessary to know whether these relations were valid for all observed values of U , D and H . Data are presented in table 2, parts 2a, 2b and 2c, and their corresponding graphs. It is seen that the formula is not ideal since patients with the same value of U/HD^3 but different values of, say, U did not have an identical outcome. A second weakness of the data is the slight overlap, in values of the formula, between patients grouped according to their D values.

Data concerning the possible influence of certain other factors on these relations are indicated in table 2, parts 3 to 12, and their corresponding graphs. The results of blood culture, the extent and character of the pulmonary involvement, and the age each influenced one or more of the indexes of outcome, the quality of the alteration being in agreement with expectancy (e.g., the mortality was greater with positive than with negative blood cultures). The values of the constants a and b hence varied, but the general equation remained valid.⁸ Smaller differences in the values of a and b were observed with differences in type, season and admission temperature. Very slight or no differences were observed with differences in total leukocyte count, race, sex or the presence or absence of known concomitant conditions. Two anomalies of the complication rate are within statistical expectancy and do not vitiate the otherwise uniform results observed.

As further indexes of outcome, the duration of hospitalization and the total time the patient was febrile (from onset to the last temperature, in the absence of complication, over 99.0 F) were also studied, but no relation could be established between them and the expression U/HD^3 .

Relations between Dosage and the Defervescence—As shown in table 3 and figure 3, the number of febrile hours (F_h), between the first dose of serum and the first normal temperature reading, was a function of the rate (S/t , thousands of units per hour) of serum administration prior to the first normal temperature. Since this part of the study was

⁸ A much greater number of patients would permit quantitative studies of these factors by the method here used for D , but that is impossible with the number available in this study.

confined to the 462 patients who had a defeverescence before cure, death or the recognition of a complication, the findings cannot be interpreted as indicating that a defeverescence will follow a certain treatment, they indicate only that if a defeverescence does occur it may be expected at a given time. On the graph is indicated a line, y' , which represents the mean $\log_{10} F_h$ calculated by the method of least squares for the various values of $\log_{10} S/t$. The equation for this line (e g, for the relation

TABLE 3—*Relation Between Dosage and the Temperature Response, in the Four Hundred and Sixty-Two Patients Who Became Afebrile (99) Following Serum and Before Termination of the Disease by Cure, Death or Recognition of a Complication*

Patients are divided according to various rates of serum administration (thousands of units per hour S/t) before the first normal temperature reading. Part 1 indicates the number of patients and their average duration of continuous fever (F_h), as well as the average amount of serum (S , in thousands of units) received before the defeverescence, the average number of lobes involved and the incidence of bacteremia in patients from whom cultures were taken. Part 2 indicates the influence of the duration (in days, D) of untreated illness and of type (I, II, VII, and all others) on the relation between the rate of serum treatment and the duration of continuous fever.

Part 1

Log (S/t)	Total Number of Patients	Log of Average F_h	Average S	Average Number of Lobes	Blood Cultures, % Positive
—0.2218 to 0.6070	55	1.9345	130	1.8	6
0.6071 to 0.9564	118	1.7324	113	1.5	0
0.9565 to 1.1604	104	1.5185	115	1.4	7
1.1605 to 1.2889	39	1.5051	150	1.3	14
1.2890 to 1.3882	44	1.5424	91	1.4	8
1.3883 to 1.6941	86	1.2788	148	1.5	7
1.6942 to 2.3010	16	1.0414	150	1.5	0

Part 2

Log (S/t)	Log (Average F_h)			Log (Average F_h)			
	D 1 to D 3	D 4 to D 6	D 7 and Up	Type I	Type II	Type VII	Other Types
—0.2218 to 0.6070	1.81	1.97	2.06	1.89	2.02	1.82	2.08
0.6071 to 0.9564	1.76	1.73	1.72	1.70	1.64	1.81	1.85
0.9565 to 1.1604	1.53	1.52	1.51	1.54	1.40	1.54	1.46
1.1605 to 1.2889	1.30	1.40	1.88	1.63	1.54	1.30	1.23
1.2890 to 1.3882	1.46	1.38	1.00	1.23	1.23	1.67	1.95
1.3883 to 1.6941	1.20	1.32	1.20	1.32	1.62	1.32	1.04
1.6942 to 2.3010	1.00	1.11	0.78	0.48	1.46	0.78	1.00

between the duration of continuous fever and the rate of serum treatment) is, with the standard error indicated as a plus or minus variation,

$$(4) \log_{10} F_h = (2.1842 - 0.3621) - 0.7470 (\log_{10} S/t)$$

Table 3 presents the following data: the number of patients, the logarithm, to the base 10, of the average F_h , the average value of S , the average number of lobes involved, and the incidence of bacteremia (in studied cases) for various values of the logarithm, to the base 10, of S/t . It is seen that the relation demonstrated in the graph cannot be explained on the basis of the actual dosage (S), of the extent of pulmonary involvement or of the incidence of positive blood cultures. The second part of the table shows that the relation demonstrated in the graph was

independent of the duration of the untreated disease (D) and probably independent of the type of pneumococcus (so far as this was investigated)

The recurrence of fever and the character of the defervescence were also studied. It was found that the incidence of crisis increased with increasing values of S/t , but the incidence of recurrence of fever was virtually constant for all values of S/t . These aspects of the temperature response were also unaltered by the duration of the untreated disease (D)

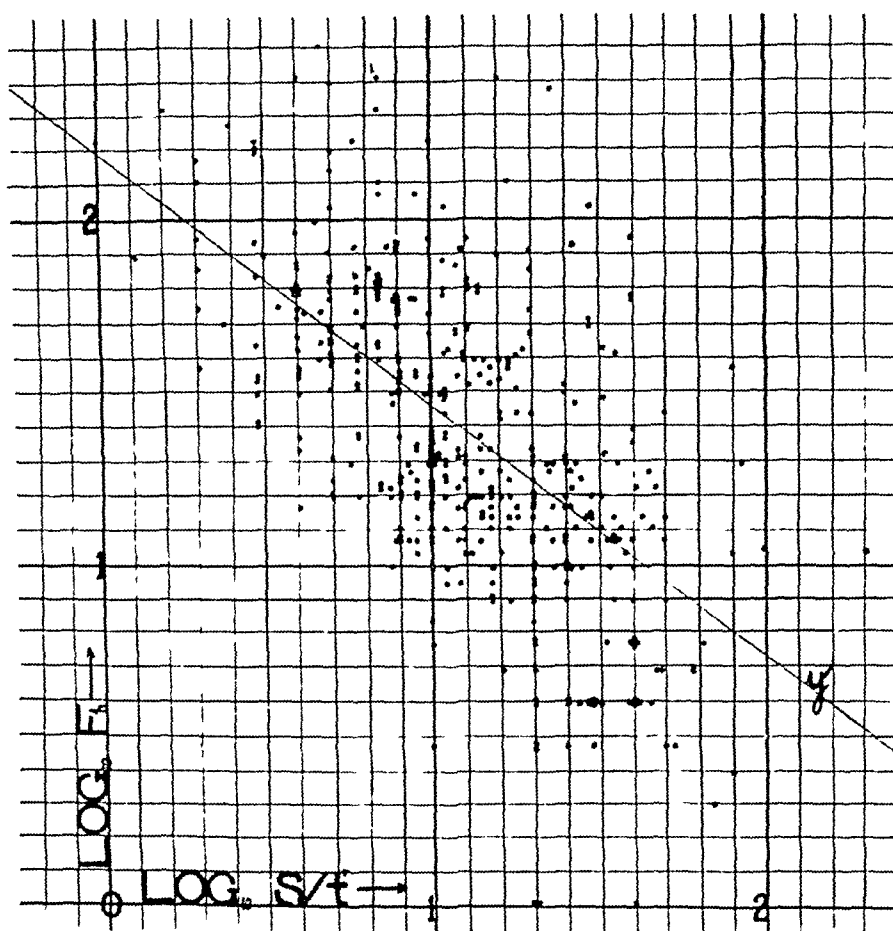


Fig 3—Relation between dosage and the temperature response S , number of thousand units of serum given before the first normal temperature, t , time in hours from the first to the last dose of that serum, F_h , number of febrile hours from the first dose of serum to the first normal temperature reading. Each point represents one patient. The line, y' , is the mean $\log_{10} F_h$ calculated by the method of least squares.

COMMENT

Bearing in mind certain limitations of the data that have been mentioned, one can clearly see from the findings that the outcome was a function of the rate of serum treatment divided by the cube of the number of days the patient was untreated (e g, U/HD^3), while the speed with which a defervescence followed the initiation of treatment

was a function of the rate of serum treatment (e g, S/t) without regard to the number of days the patient was untreated. The incompatibility of these findings is superficial.

Serum reacts specifically with materials produced by the pneumococci in the lung, these reactions occur almost exclusively, however, in the blood stream.⁹ There may be various kinds of antigen,¹⁰ but the quantitatively predominant one is the specific soluble substance, a haptene derived from the capsule of the organism. This haptene is probably

9 Drinker, C K, Enders, J F, Shaffer, M F, and Leigh, O C. Emigration of Pneumococci Type III from Blood into Thoracic Duct Lymph of Rabbits, and Survival of These Organisms in Lymph Following Intravenous Injection of Specific Antiserum, *J Exper Med* **62** 849-860 (Dec) 1935

10 Neufeld, F. Ueber die Agglutination der Pneumokokken und über die Theorien der Agglutination, *Ztschr f Hyg u Infektionskr* **40** 54-72, 1902. Neufeld, F, and Handel, L. Weitere Untersuchungen über Pneumokokken-Heilsera, *Arb a d k Gsndtsamte* **34** 293-304, 1910. Dochez, A R, and Gillespie, L G. A Biologic Classification of Pneumococci by Means of Immunity Reactions, *J A M A* **61** 727-732 (Sept 6) 1913. Dochez, A R, and Avery, O T. Varieties of Pneumococcus and Their Relation to Lobal Pneumonia, *J Exper Med* **21** 114-132, 1915. Avery, O T. A Further Study of the Biologic Classification of Pneumococci, *ibid* **22** 804-819, 1915. Lister, F S. Specific Serological Reactions with Pneumococci from Different Sources, Publication 3, South African Institute of Medical Research, Johannesburg, W E Hortor & Co, 1914. Heidelberger, M, and Avery, O T. The Specific Soluble Substance of Pneumococcus, *J Exper Med* **38** 73-79 (July) 1923. Avery, O T, and Heidelberger, M. Immunological Relationships of Cell Constituents of Pneumococcus, *ibid* **38** 81-85 (July) 1923. Heidelberger, M, and Avery, O T. The Soluble Specific Substance in Pneumococcus, *ibid* **40** 301-316 (Sept) 1924. Avery, O T, and Heidelberger, M. Immunological Relationships of Cell Constituents of Pneumococcus, *ibid* **52** 367-376 (Sept) 1925. Julianelle, L A, and Reimann, H A. The Production of Purpura by Derivatives of the Pneumococcus. I. General Considerations of the Reaction, *ibid* **43** 87-95 (Jan) 1926. Mair, W. Purpura Producing Substance in Pneumococcus and Heritable Susceptibility of Mice, *J Path & Bact* **31** 215-219 (April) 1928. Cooper, G, Edwards, M, and Rosenstein, C. Separation of Types Among Pneumococci Hitherto Called Group IV and Development of Therapeutic Antisera for Those Types, *J Exper Med* **49** 461-474 (March) 1929. Pittman, M, and Falls, T S. Studies on Respiratory Diseases. Some Relations Between Extracts, Filtrates, and Virulence of Pneumococci, *J Bact* **19** 327-361 (May) 1930. Enders, J F. Type Specific Substance Distinct from Specific Carbohydrate in Pneumococcus Type I, *J Exper Med* **52** 235-252 (Aug) 1930. Tillett, W S, Goebel, W F, and Avery, O T. Chemical and Immunological Properties of Species-Specific Carbohydrate of Pneumococci, *ibid* **52** 895-900 (Dec) 1930. Wadsworth, A, and Brown, R. Chemical and Immunological Studies of Pneumococcus. Specific Antigenic Carbohydrate of Type I Pneumococcus, *J Immunol* **21** 245-253 (Sept) 1931. Goodner, K. Development and Localization of Dermal Pneumococcic Lesion in Rabbit, *J Exper Med* **54** 847-858 (Dec) 1931. Cooper, G, Rosenstein, C, Walter, A, and Peizer, L. Further Separation of Types Among Pneumococci Hitherto Included in Group IV and Development of Thera-

distributed throughout the body¹¹ but is in greatest concentration at the site of infection¹² Though probably not toxic itself, its relatively great concentration and its avidity for immune bodies cause it to act as a buffer between the natural defenses of the body and the toxic substances of the organisms themselves,¹³ which the defenses must destroy to insure the survival of the patient The specific soluble substance might be called the glue binding the disease to the patient

By demonstrating that there was a logarithmic diminution in the effectiveness of serum with increasing time illness was untreated, we have not directly proved that there was a logarithmic increase in the need for serum This would, however, be a plausible deduction Furthermore, the materials with which serum reacts are formed by organisms whose metabolism is probably a function of their growth curve Since the latter is logarithmic *in vitro*, some sort of logarithmic increase in the products of metabolism should be expected

peutic Antisera for These Types, *ibid* **55** 531-554 (April) 1932 Gundel, M, and Schwarz, F K T Ueber die Typendifferenzierung und Epidemiologie der Gruppe X der Pneumokokken, *Ztschr f Hyg u Infektionskr* **113** 498-522, 1932 Goodner, K Effect of Pneumococcus Autolysates upon Pneumococcus Dermal Infection in Rabbits, *J Exper Med* **58** 153-160 (Aug) 1933 Avery, O T, and Goebel, W F Chemoimmunological Studies on Soluble Specific Substance of Pneumococcus Isolation of Acetyl Polysaccharide of Pneumococcus Type I, *ibid* **58** 731-755 (Dec) 1933 Oram, F Pneumococcus Leucocidin, *J Immunol* **26** 233-246 (March) 1934 Todd, E W Comparative Serological Study of Streptolysins Derived from Human and Animal Infections, with Notes on Pneumococcal Haemolysin, Tetanolysin, and Staphylococcus Toxin, *J Path & Bact* **39** 299-321 (Sept) 1934

11 Cole, R L Antipneumococcus Immune Bodies, *J Exper Med* **26** 453-475 (Oct) 1917 Dochez, A R Elaboration of Specific Soluble Substance, *ibid* **26** 477-493 (Oct) 1917 Cole, R Serum Therapy of Pneumococcic Pneumonia, *J A M A* **109** 2059-2060 (Dec 18) 1937

12 Graesser, J B Specific Soluble Substance of Pneumococcus in Lungs of Dogs Recovered from Experimental Lobar Pneumonia, *Proc Soc Exper Biol & Med* **32** 386-389 (Nov) 1934 Nye, R N, and Harris, A H Viable Pneumococci and Pneumococcic Specific Soluble Substance in Lungs from Cases of Lobar Pneumonia, *Am J Path* **13** 749-767 (Sept) 1937

13 Sia, R H P Studies on Pneumococcus Growth Inhibition Specific Effect of Pneumococcus Soluble Substance on Growth of Pneumococci in Normal Serum-Leukocyte Mixtures, *J Exper Med* **43** 633-645 (May) 1926 Wadsworth, A B, and Sickles, G M Effect of Type I Pneumococcus Culture Broth on Phagocytic Action of Type I Pneumococcus Serum, *J Immunol* **14** 321-328 (Dec) 1927 Sickles, G M Further Observations on Effect of Type I Pneumococcus Culture Broth on Phagocytic Action of Type I Pneumococcus Serum, *ibid* **14** 329-336 (Dec) 1927 Ward, H K Observations on Phagocytosis of Pneumococcus by Human Whole Blood Normal Phagocytic Titre, and Anti-Phagocytic Effect of Specific Soluble Substance, *J Exper Med* **51** 675-684 (May) 1930 Boerner, F, and Mudd, S Determination of Phagocytic Power of Whole Blood or Plasma-Leukocyte Mixtures for Clinical or Experimental Purposes, *Am J M Sc* **189** 22-35 (Jan) 1935

Although the production of fever is probably a complex mechanism, we shall assume, for the sake of simplicity, that in this instance it is activated by the presence in the blood stream of substances with which serum may react specifically. The fact that the relation between treatment and the speed with which a defervescence followed its initiation was independent of the duration of untreated illness requires that the average concentration of those substances (with which serum reacts) must be virtually constant throughout the disease¹⁴

At first glance, then, it may seem impossible that the total amount of material—largely specific soluble substance—should increase logarithmically while the blood concentration remained virtually constant. This incompatibility is resolved, however, by the assumption of a threshold mechanism regulating the blood concentration, in conjunction with a diminishing rate of absorption from the lung¹⁵

One may conclude that there are definite laws governing the effectiveness of serum treatment as regards outcome and the defervescence and that they have a rational foundation in theory.

Application of these laws to the treatment of the patient requires that their quantitative statement (as in the four equations that have been given) be derived from study of larger numbers of patients than available in this investigation. Certain generalizations, however, may be made at this time. It is probable that excellent results may be expected if the patient is given, for the cube of the number of days untreated, about 10,000 units of serum *per hour*, the duration of treatment being regulated by the response of the patient, e. g., 270,000 units *per hour* for a patient treated on the third day of his illness. Such doses may exceed the amounts one can actually give. One tenth to one one-hundredth of that dose might give good results in certain patients, but one one-thousandth or less would probably be of little if any benefit. It must be noted that there is no statement of the total desired dose. We feel that this cannot be estimated, rather, a definite amount *per hour* should be given until the desired effects are seen. The early defervescence that may follow the larger doses does not necessarily indicate that the patient's stores of antigen have been exhausted but indicates only that serum was administered more rapidly than the blood level of antigen could be restored by absorption from the reservoir in the lung. Hence if after the defervescence a relapse leads to the resumption of treatment, attention should be paid to the fact that the value of H has been increasing during the

14 Nonspecific temperature reactions usually occur almost immediately after treatment is begun, and for this reason we think that the reactions here noted are specific rather than nonspecific.

15 Wang, T. T., and Van Allen, C. M. Concentration of Congo-Red in Blood After Absorption from Pneumonic Lung, *Proc Soc Exper Biol & Med* 30 814-816 (March) 1933.

untreated pause, unless extra amounts of serum are given, equal to the amount that would have been given during the interruption of treatment, the numerical value of the expression U/HD^3 will be decreased

SUMMARY

The effects of type-specific serum on the outcome of pneumococcic pneumonia have been studied in 513 treated patients, unselected except as regards adequacy of their clinical records. The outcome was found to be a function of the treatment, according to the general equation

$$\% \text{ Outcome} = a + b (\log_{10} U/HD^3)$$

in which a and b are constants, U is the total dose in thousands of units of commercial antipneumococcus serum, H is the number of hours between the first and the last dose of serum and D is the number of days from the onset of pneumonia to the first dose of serum. The values of a and b varied depending, of course, on the index of outcome under consideration—death, complication or survival without complication. Minor and expected variations also occurred with variations in type, pulmonary involvement, bacteremia et al, but the general statement of the law was valid under all circumstances.

The ability of serum to hasten the defervescence was studied in all (462) patients who had a defervescence between the first dose of serum and the recognition of a complication or termination of the disease. The speed with which a defervescence followed initiation of treatment was found to be a function of the rate of that treatment, according to the general equation

$$\text{Log}_{10} F_h = a + b (\log_{10} S/t)$$

in which a and b are constants, F_h is the number of febrile hours from the first dose of serum to the first normal temperature, S is the amount of serum in thousands of units given before the first normal temperature and t is the time in hours from the first to the last dose of that serum. This relation was found to be independent of the duration of untreated illness, type, pulmonary involvement and bacteremia.

The theoretic and the practical significance of the findings are mentioned.

Dr J Leonard Moore assisted in the preparation of this paper.

STUDIES ON OLD AGE PNEUMONIA

II PROPHYLACTIC EFFECT OF PNEUMOCOCCUS POLYSACCHARIDE AGAINST PNEUMONIA

PAUL KAUFMAN, M D

WITH THE TECHNICAL ASSISTANCE OF A KAEFELY, M D , C O'BRIEN, M D ,
C BURNSTEIN, S KAUFMAN KLING, B A , AND W DMITRUK
NEW YORK

The purpose of this paper is to report on work done since 1937 on active immunization with antigenic polysaccharides against pneumonia. The group immunized were inmates of the New York City Home. Most of them were above the age of 50 and a great majority between the ages of 60 and 80 (table 1). There were several reasons why this group was chosen for the experiment. First They have a high incidence of pneumonia, mortality and case fatality rate. Second Repeated attacks of pneumonia occur frequently. Third They could be kept under observation for years, as the turnover in the Home is limited and those who were discharged could be followed up, moreover a great many of them were readmitted to the Home and further observed. Fourth Those who contracted pneumonia were transferred to the supervising hospital of the New York City Home for Dependents (which was previously the Central and Neurological Hospital and at present is the Welfare Hospital), where they could be clinically studied.

HISTORY AND LITERATURE OF PNEUMOCOCCUS POLYSACCHARIDES

Kraus¹ and Auld² discovered almost simultaneously in 1897 the presence of specific precipitable substances in the germ-free culture filtrates of certain bacteria. Kraus in cultures of material from persons with cholera, typhoid fever and bubonic plague and Auld in pneumococcus cultures. The latter also proved that these substances have antigenic properties. Neufeld³ (1902) showed that the bile solutions

From the II Medical Division and Pathological Laboratories of Welfare Hospital

This work was started at the Central and Neurological Hospital and the New York City Home for Dependents

1 Kraus, R. *Wien klin Wchnschr* **10** 736, 1897

2 Auld, A. C. *Brit M J* **1** 775, 1897

3 Neufeld, F. *Ztschr f Hyg u Infectiönskr* **40** 54, 1902

of pneumococcus cultures give similar results, and Wadsworth⁴ (1903) reported the same thing in regard to the filtrates of those organisms in salt solutions

Dochez and Avery⁵ (1917) in their report about the specific soluble substance showed that the presence of this substance is not due to bacterial death and disintegration but represents the extrusion into the medium of bacterial substances during the life process of the organism. They also demonstrated the presence of the specific soluble substance in the serum and urine of patients with pneumonia and showed that its presence in abundance indicates a grave prognosis.

Heidelberger with Avery⁶ (1923) studied the chemical constituents of these substances in the different types of pneumonia and showed that the combination of the carbon, hydrogen and oxygen to form varying percentages of carboxyl, acetyl and other radicals and the combination of these groups with the different sugars determine the specificity of the types of pneumococci. Type I has nitrogen and has acidic and basic properties, and they found that it had no antigenic effect. Type II is dextrorotatory and weakly acid and has no nitrogen. Type III is levorotatory and strongly acid and has no nitrogen. Heidelberger and Kendall⁷ (1935) worked out quantitative methods for the determination of the amount of precipitable substances from cultures of pneumococci of type III by means of therapeutic serum. The same authors with Scherp⁸ (1936) further analyzed the physicochemical qualities of the polysaccharide. They showed that it is thermolabile, and this characteristic may be explained as a partial depolymerization. On the basis of analytic data, these authors assumed that chemically it is a trisaccharide unit for the SI molecule, containing two molecules of uronic acid (possibly both galactouronic) and two atoms of nitrogen.

Avery and Goebel⁹ (1933) described an acetyl polysaccharide of the pneumococcus, which, contrary to Heidelberger and Avery's, was antigenic for mice.

From these and other pertinent discoveries it seemed apparent that the cell body of the pneumococcus contains the species-specific nucleoproteins while the capsule contains the type-specific carbohydrates. Both have antigenic properties, but the nucleoproteins react with all

4 Wadsworth, A. J. *M. Research* **10** 228, 1903

5 Dochez, A. R., and Avery, O. T. *J. Exper. Med.* **26** 477, 1917

6 Heidelberger, M., and Avery, O. T. *J. Exper. Med.* **38** 73, 1923

7 Heidelberger, M., and Kendall, F. E. *J. Exper. Med.* **61** 559 and 563, 1935

8 Heidelberger, M., Kendall, F. E., and Scherp, H. W. *J. Exper. Med.* **64**, 559, 1936

9 Avery, O. T., and Goebel, W. F. *J. Exper. Med.* **58** 731, 1933

varieties (group antigens) while the capsular polysaccharides precipitate only the specific type of pneumococcus from which they are extracted. They are partial antigens or "haptens" in Landsteiner's¹⁰ or "residual antigens" in Zinsser's¹¹ meaning.

A further step in the investigation of these substances was made when Francis and Tillett¹² (1930) noted that intracutaneous injections of polysaccharides produced not only a homologous but a heterologous stimulation of antibodies^{12a}. This heterologous action was confirmed by Finland and Sutliff¹³ (1932) and by Felton, Sutliff and Steele¹⁴ (1935).

Felton¹⁵ (1932) also isolated a water-soluble substance from pneumococci of types I and II, which was a fraction apparently nonpolysaccharide and probably nonprotein, contained no acetyl radical and still was antigenic for mice. Later he used various methods for the isolation of the specific soluble substances, precipitating them repeatedly with large volumes of alcohol, some after alkaline treatment and others from the acid-soluble fraction as in the original Heidelberger and Avery method. He also used calcium phosphate for precipitation. His purification procedure was to dissolve the crude product at 0 C at p_H of 3 or less or even in concentrated hydrochloric acid, or in 1:1 sulfuric acid and repeated precipitation with large amounts of alcohol. The final product contained various amounts of dextrose and nitrogen and was similar in chemical characteristics to the polysaccharide of Heidelberger and Avery. Felton reported that he obtained immunity in white mice and in a small number of human beings.

Felton in collaboration with Ekwurtzel, Simmons and Dublin¹⁶ (1938) reported four experiments on active immunization with this substance in the CCC camps. The first three experiments were not considered sufficiently controlled to warrant any definite conclusion. In the fourth experiment inoculations were done on 10,740 men in New England and 18,494 in West Coast camps. Since the time of their experiments was short (in some cases sixty-eight and three-tenths days and in others one hundred seventeen and four-tenths days), they took into consideration not only the number of men but also the time of

10 Landsteiner, L. *New England J Med* **215** 1199, 1936

11 Zinsser, H., and Parker, J. T. *J Exper Med* **37** 275, 1923

12 Francis, T., and Tillett, W. S. *J Exper Med* **52** 573, 1930

12a They explained that on the basis of previous pneumococcal infections

13 Finland, M., and Sutliff, W. D. *J Exper Med* **55** 853, 1932

14 Felton, L. D., Sutliff, W. D., and Steele, B. F. *J Infect Dis* **56** 101, 1935

15 Felton, L. D. *J Immunol* **23** 405, 1932

16 Felton, L. D., Ekwurtzel, G. M., Simmons, J. S., and Dublin, L. I. *Pub Health Rep* **53** 1877, 1938

exposure The opportunity for infection for a group of persons is proportional to the product of the number of persons and the number of days each is exposed during the period considered When this product is divided by 365, the result can be expressed as "years of life exposed to the risk of infection" The years of life exposed were 3,461 in the West Coast camps and 3,153 for the New England camps The incidence rate in the West Coast camps was 1.73 in the inoculated against 15.69 in the noninoculated group per thousand years of life The New England camps showed an incidence of 4.34 cases in the inoculated group against 7.28 in the noninoculated In other words, the incidence rate was about nine times higher in the control group than in the inoculated in the West Coast camps, while in the New England camps it was only about twice as high According to the report of Felton and his co-workers, "the difference in case ratio between inoculated enrollees in the New England camps and those in the West Coast camps cannot be definitely accounted for" Owing to the circumstances inherent to their experiments, the number of deaths was considered too few to justify any conclusions with regard to the effect of the antigen on the mortality or case fatality rates

MATERIALS USED IN THIS EXPERIMENT

The antigen which we used was a capsular polysaccharide prepared as follows ¹⁷ Broth cultures of type I and type II pneumococci are centrifuged for forty-eight hours The supernatant fluid is passed through ultrafiltration The soluble specific substance is precipitated by the repeated use of large volumes of alcohol in a reaction neutral to slightly acid The soluble carbohydrates are then tested for their purity and antigenic properties The material employed was a combination of type I and type II polysaccharides Chemically the dextrose and nitrogen content was approximately that of the specific soluble substance of Heidelberger and Avery

METHOD OF THE EXPERIMENT

First Year—In the winter of 1937-1938, 1,000 persons were immunized with 0.5 cc of this solution containing 1 mg of each active substance, and 1,120 persons were kept as controls The injection of the antigen was given subcutaneously in the deltoid region The previous history of each person was taken with special reference to antecedent pneumonia or infections of the upper respiratory tract On every twentieth person the precipitin and mouse-protective value of the blood was determined before immunization ¹⁸ The preliminary work included quantitative and qualitative blood counts on these members of the immunized group We had

¹⁷ The antigen used was prepared first by ourselves and later by a commercial laboratory At present, through the courtesy of Dr Felton a type I, II, III antigen—as prepared in the United States Public Health Service Laboratory, Washington D C—is used

¹⁸ Reports on the immunologic studies of these experiments will be published elsewhere

records of previous physical examinations, temperature, pulse rates and blood pressure for every immunized person. When it seemed necessary, however, physical examinations were given before immunization.

The test for precipitin and mouse-protective value of the serums of the immunized was repeated after eight days, after twenty-one days and after three to four months.

Protocols were kept of both the immunized and the control group, in which the aforementioned data, reactions after immunizations and further information, as to contraction of pneumonia or other diseases were recorded. Persons who left the institution were further observed by a follow-up system.

The hospital record of every patient with pneumonia showed whether he belonged to the immunized or to the control group. Special attention was paid to such patients with regard to time, extension and duration of pneumonia.

The period of observation was continuous from Nov. 1, 1937 to November 1939.

Second Year—In 1938-1939 the same method was used except that while in the first year the inoculated persons volunteered for the injections, now they were taken as follows. Five hundred new patients were divided in such a way that every other one was chosen for the inoculation and the alternates were kept as controls.

TABLE 1—*Age Distribution of the Inoculated and Control Groups*

Age Distribution	Inoculated Group on Basis of 1,750		Control Group on Basis of 1,870	
	Number of Persons	Per Cent	Number of Persons	Per Cent
Under 40 to 40	26	1.5	73	3.9
50 to 59	315	18.0	355	19.0
60 to 69	639	36.5	692	37.0
70 to 79	534	30.5	591	31.6
80 and over	236	13.5	159	8.5

This group was given 0.5 cc. containing 1 mg. each of type I and type II of the active substance. Another 1,000 were taken from the old inmates and divided into two groups of 500 each. Five hundred were inoculated with 10 cc. containing 2 mg. of each active substance. The 500 who had been used as controls the previous year were again used as controls.

RESULTS

Age Distribution of Immunized and of Control Group—The age distribution of the inoculated and of the control group is given in table 1. This shows that in the immunized group the age distribution was as follows: 36.5 per cent between the ages of 60 and 69 years, 30.5 per cent between 70 and 79 years, 18 per cent between 50 and 59 years, 13.5 per cent 80 years or over and 1.5 per cent 40 years or below. In the control group the age distribution was 37 per cent between 60 and 69 years, 31.6 per cent between 70 and 79 years, 19 per cent from 50 to 59 years, 8.5 per cent 80 years or over and 3.9 per cent were 40 years or below. It can be seen that both groups had about the same age distribution. For equalizing purposes the general mortality rates from all causes were checked for the immunized and for the control group and found to be essentially the same.

*Effect on Incidence and Mortality Among Immunized Group Compared with Control Group*¹⁹—First Year In the first year the number of cases of pneumonia among the 1 000 immunized persons was 14 giving an incidence rate of 14 per thousand. The number of deaths in the immunized group was 8, giving a mortality rate of 8 per thousand. Among the 1 120 nonimmunized there were 63 cases of pneumonia making the incidence 56 per thousand. The number of deaths among the 1 120 controls was 47 making a mortality rate of 42 per thousand (table 2)

TABLE 2—*Incidence and Mortality Rates Among Inoculated and Noninoculated in the First and in the Second Year of Observation*

	Number of Persons	Number of Cases of Pneumonia	Incidence Rate per Thousand	Number of Deaths	Mortality Rate per Thousand
1937-1938					
Inoculated	1,000	14	14	8	8
Noninoculated	1,120	63	56	47	42
1938-1939					
Inoculated	750	9	12	5	6.6
Noninoculated	750	41	55	20	26.6

TABLE 3—*Analysis of Incidence of Pneumonia in 1938 and 1939 Among Inoculated and Control Groups*

	No of Persons	No of Cases of Pneu- monia	Incidence, %	Standard Deviation of Per- centage	Difference of Per- centage	Standard Deviation of Per- centage Difference	Critical Ratio	Cer- tainty
1937-1938								
Inoculated	1 000	14	0.014	± 0.004	0.042	± 0.009	$\frac{\pm 0.042}{\pm 0.009} = \pm 4.7$	100%
Noninoculated	1 120	63	0.056	± 0.008				
1938-1939								
Inoculated	750	9	1.2	± 0.004	0.043	± 0.00984	$\frac{\pm 0.043}{\pm 0.00984} = \pm 4.38$	100%
Noninoculated	750	41	5.5	± 0.009				

Second Year The second year there were 9 cases of pneumonia among the 750 immunized persons and 41 among the 750 nonimmunized, making the incidence rates 12 per thousand in the immunized group and 55 per thousand in the control group. The number of deaths among the 750 immunized persons was 5 making a mortality rate of 6.6 per thousand. Among the 750 nonimmunized the number of deaths was 20 making a rate of 26.6 per thousand (table 2)

19 A sample analysis of the incidence rates is given in table 3 which shows a critical ratio of 4.7 for the year 1938 and one of 4.38 for the year 1939

Subdivision of Groups in Second Year As was mentioned before, in the second year the subjects were divided into two groups Two hundred and fifty new patients received 1 mg each of type I and type II active substance, and 500 received 2 mg each There were 4 cases of pneumonia with 2 deaths in the group of 250 and 5 cases with 3 deaths

TABLE 4—*Comparison of Incidence and Mortality Rates of Those Receiving One Inoculation of 1 Mg and Those Receiving Two Inoculations of 1 Mg Each of Active Substance (1938-1939)*

Inoculated	No of Persons	No of Inoculations	Amount of Poly saccharide, Mg	No of Instances of Pneumonia	Incidence per Thousand	No of Deaths	Mortality per Thousand
Group I	250	1	1	4	16	2	8
Group II	500	2	2	5	10	3	6
Controls							
Group I	250			15	60	8	32
Group II	500			26	52	12	24

TABLE 5—*Summary of Incidence, Mortality and Case Fatality of Pneumonia During Two Years of Experiments*

	No of Persons	No of Instances of Pneu- monia	Incidence, % of Pneumonia	Standard Deviation of % of Pneumonia	Difference of % of Pneumonia	Standard Deviation of % of Difference	Critical Ratio	Cer- tainty
Incidence per Thousand Persons								
Inoculated	1,750	23	1.4	0.003	4.2	0.0067	$\frac{\pm 0.042}{\pm 0.0067} = \pm 6.3$	100%
Noninoculated	1,870	104	5.6	0.006				
Mortality per Thousand Persons								
			No of Persons		No of Deaths		Rate per 1,000	
Inoculated			1,750		13		7	
Noninoculated			1,870		67		35.8	
Fatality per Hundred Cases								
	No of Cases of Pneu- monia	No of Deaths	Case Fatality, % of Deaths	Standard Deviation of % of Deaths	Difference of % of Deaths	Standard Deviation of % of Difference	Critical Ratio	Cer- tainty
Inoculated	23	13	0.57	0.099	0.07	0.11	$\frac{\pm 0.07}{\pm 0.11} = \pm 0.627$	73%
Noninoculated	104	67	0.64	0.048				

in the group of 500 In the smaller control group there were 15 cases of pneumonia with 8 deaths and in the larger control group 26 cases with 12 deaths As can readily be seen, there was no significant difference in the incidence and mortality rates between those receiving two injections of 1 mg each and those receiving one injection of 1 mg (table 4)

Total Period of Observation (table 5)—Among the total 1,750 inoculated persons there were 23 cases of pneumonia, making the rate

13.13 per thousand. Among the total 1,870 controls there were 104 cases, making the rate 55.66 per thousand. There were 13 deaths in the immunized group, making the mortality rate 7.4 per thousand. In the control group the number of deaths was 67, making a mortality rate of 35.8 per thousand.

Effect of Immunization on Case Fatality Rates—The number of deaths among the 23 inoculated patients with pneumonia was 13, making a case fatality rate of 57 per cent. In the control group the number of deaths among 104 patients with pneumonia was 67, making a case fatality rate of 64 per cent. The statistical analysis of these figures which is given in table 5 shows that the critical ratio is 0.627 and the percentage of certainty is 73. Nevertheless it does not seem justified to draw conclusions from the case fatality rate calculated on such a small number of deaths.

TABLE 6—*Pneumonia Mortality and Incidence per Thousand Years of Life*

	No of Persons	Years of Life Exposed	No of Instances of Pneu- monia	Incidence Rate	No of Deaths	Mortality Rate
Inoculated						
1938	1,000	1,890.4	14	7.4%	8	4.2%
1939	750	708.9	9	12.6%	5	7.0%
Total	1,750	2,599.3	23	8.8% of total	13	5.0% of total
Noninoculated						
1938	1,120	2,092.7	63	30.1%	47	22.4%
1939	750	684.2	41	39.9%	20	29.2%
Total	1,870	2,776.9	104	37.4% of total	67	24.1% of total

Comparison of Incidence and Mortality Rates Observed in Two Years of Experiment With Those of Previous Ten Years—Since many of the persons who were under observation in these experiments were in the institution for years and represented a cross section of the total, we had a fairly accurate estimate of their previous incidence and mortality rates. If the rates for the past ten years are compared with those of these two years' experiments, it is seen that whereas the average rate of incidence in the previous ten years was 57 per thousand and the mortality rate was 28.3 per thousand, in these two years of observation the incidence rate among the immunized came down to 13.12 per thousand and the mortality rate to 7.4 per thousand.

Incidence and Mortality Rates Considered on Basis of Years of Life Exposed—The incidence and mortality rates in the previous paragraphs are calculated per thousand. For comparison it seemed worth while to compute the incidence and mortality rates on the basis of a thousand years of life (as explained in the section on the experiments of Felton, Ekwurtzel, Simmons and Dublin). This computation is shown in table 6.

TABLE 7—*History of Patients with Pneumonia in the Inoculated Group During the Two Years*

Case Number, Sex, Age, Years	No of Days from Inoculation to Onset of Pneumonia	Type of Organism (Culture of Sputum and Blood)	Physical Diagnosis	Röntgentographic Findings	Blood Count	Duration of Pneu- monia, Days	Results	Autopsy Observations or Comments
1 F 70	4	No pneumo- cocci of types I through XXXII	Lobar pneumonia, (LLL, RLL)	Irregular, patchy, confluent clouding of lower left portion of chest and base of right lung suggestive of bronchopneumonic involvement	Hemoglobin, 85% White blood cells, 15,600 Red blood cells, 4,600,000 Polymorphonuclears, 91% Lymphocytes, 9%	12	Recovery	
2 F 46	27	No organism	Lobar pneumonia (RML)	Massive consolidation in right middle lobe area with some clouding at base, perhaps pleural in origin	Hemoglobin, 85% White blood cells, 25,400 Red blood cells, 4,500,000 Polymorphonuclears, 91% Lymphocytes, 9%	10	Recovery	
3 M 78	32	No pneumo- cocci of types I through XXXII, diplococci, streptococci, no tubercle bacilli	Bronchial pneumonia (RML, LLL)	Patchy confluent pneumonic changes in both midlobe regions	Hemoglobin, 53% White blood cells, 7,700 Red blood cells, 3,700,000 Polymorphonuclears, 73% Lymphocytes, 27%	8	Death	
4 F 62	98	Type XIX	Lobar pneumonia (RLL)	Irregular central consolidation at base of right lung, rest of lungs clear	Hemoglobin, 76% White blood cells, 10,700 Red blood cells, 4,100,000 Polymorphonuclears, 75% Lymphocytes, 25%	12	Recovery	
5 M 69	123	No organisms	Bronchial pneumonia (LLL)		Hemoglobin, 90% White blood cells, 9,400 Red blood cells, 4,660,000 Polymorphonuclears, 75% Lymphocytes, 21%	18	Recovery	
6 M 66	132	Type III	Lobar pneumonia (RLL)	Localized patchy consolidation at base of right lung	Hemoglobin, 90% White blood cells, 12,800 Red blood cells, 4,660,000 Polymorphonuclears, 83% Lymphocytes, 16%	12	Recovery	
7 M 70	137	Type III, blood cul- ture positive	Bronchial pneumonia (RML, RLL)		Hemoglobin, 87% White blood cells, 11,600 Red blood cells, 4,400,000 Polymorphonuclears, 76% Lymphocytes, 17%	18	Death	

8 M 58	141	Type III	Lobar pneumonia with pleural effusion (LLL)	Clouding of entire left chest and deviation of heart to right, indicating pleural effusion	Hemoglobin, 90% White blood cells, 29,300 Red blood cells, 4,600,000 Polymorphonuclears, 82% Lymphocytes, 14%	2	Death	
9 F 69	176	Cultures not made	Bronchial pneumonia (RML)	No roentgen examination	Hemoglobin, 80% White blood cells, 13,600 Red blood cells, 4,370,000 Polymorphonuclears, 75% Lymphocytes, 24%	1	Death	Autopsy pulmonary congestion, lobar pneumonia, cardiac hypertrophy, dilatation of heart, right coronary sclerosis, myocardial fibrosis, hypertensive kidney atrophy of uterus and ovaries decrease in size of parenchymatous organs
10 M 85	191	No organisms	Lobar pneumonia (RLL, LLL)	Irregular, patchy confluent pneumonia, changes in both lower lobes	Hemoglobin, 90% White blood cells, 28,600 Red blood cells, 4,800,000 Polymorphonuclears, 90% Lymphocytes, 10%	2	Death	
11 F 68	225	Type II, blood culture positive	Bronchial pneumonia (LLL)	No roentgen examination	Hemoglobin, 83% White blood cells, 9,800 Red blood cells, 4,600,000 Polymorphonuclears, 80% Lymphocytes, 19%	6	Death	Autopsy bronchopneumonia, hypertrophy of heart, congestion and fatty degeneration of liver and arteriosclerosis, left kidney, congenital hypoplasia, right kidney
12 M 75	236	Cultures not made	Bronchial pneumonia (RLL)	At base of right lung, irregular patchy pneumonia exudate, dilatation of arch and descending aorta, a soft basic shadow projecting laterally from left cardiac border	Hemoglobin, 80% White blood cells, 12,800 Red blood cells, 4,220,000 Polymorphonuclears, 85% Lymphocytes, 15%	7	Recovery	
13 M 79	253	Long chained streptococci	Bronchial pneumonia	One small calcified area at base of right lung and small area in left hilus indicating pulmonary tuberculous infection, no pulmonary infiltration or consolidation	Hemoglobin, 88% White blood cells, 9,800 Red blood cells, 4,510,000 Polymorphonuclears, 81% Lymphocytes, 19%	12	Death	Autopsy lobular pneumonia, cardiac hypertrophy, coronary sclerosis, horseshoe kidney
14 M 48	292	No tubercle bacilli, no pneumococci of types I through XIV	Bronchial pneumonia (RML, RLL)		Hemoglobin, 90% White blood cells, 8,600 Red blood cells, 4,760,000 Polymorphonuclears, 66% Lymphocytes, 29%	6	Death, 10th day	
15 F 50	307	Type I, blood culture negative	Bronchial pneumonia (RLL)	Central consolidation occupying inner half of lower lobe of right lung, rest of lungs clear	Hemoglobin, 82% White blood cells, 15,800 Red blood cells, 4,400,000 Polymorphonuclears, 85% Lymphocytes, 13%	10	Recovery	
16 M 70	324	Type III, blood culture positive	Lobar pneumonia (LML)	Opacity in right side of chest between second and fifth ribs irregular exudative nodules in first intercostal space	Hemoglobin, 90% White blood cells, 14,700 Red blood cells, 4,500,000 Polymorphonuclears, 89% Lymphocytes, 11%	8	Death	

TABLE 7—History of Patients with Pneumonia in the Inoculated Group During the Two Years—Continued

Case Number, Sex, Age, Years	No of Days from Inoculation to Onset of Pneumonia	Type of Organism (Culture of Sputum and Blood)	Physical Diagnosis	Roentgenographic Findings	Blood Count	Duration of Pneumonia, Days	Results	Autopsy Observations or Comments
17 M 81	331	No organism	Bronchial pneumonia (LLL)	No pulmonary consolidation delineated	Hemoglobin, 72% White blood cells, 8,600 Red blood cells, 3,800,000 Polymorphonuclears, 79% Lymphocytes, 18%	5	Death	Autopsy hypostatic pneumonia
18 M 41	342	No pneumo cocci of types I through XXXII, streptococci in small and large chains	Bronchial pneumonia (LLL)		Hemoglobin, 90% White blood cells, 10,200 Red blood cells, 4,520,000 Lymphocytes, 18%	11	Recovery	
19 M 67	353	No organisms	Bronchial pneumonia (RLL, LLL)		Hemoglobin, 90% White blood cells, 9,200 Red blood cells, 4,520,000 Polymorphonuclears, 57% Lymphocytes, 40%	14	Death, 18th day	Autopsy confluent lobular pneumonia (RLL, RUL, possibly LLL)
20 M 85	361	No organisms	Bronchial pneumonia (RLL)	Irregular patchy consolidation in lower lobe of right lung, rest of lung clear	Hemoglobin, 90% White blood cells, 13,800 Red blood cells, 4,630,000 Polymorphonuclears, 90% Lymphocytes, 9%	6	Death	Autopsy no effusion in pleural cavities, many pleural adhesions on the right, pulmonary fibrosis in both lungs, more to right, lobular pneumonia (RLL) showed considerable arteriosclerotic changes in large pulmonary vessel
21 M 75	364	Type III	Bronchial pneumonia (RLL)	Irregular confluent consolidation at base of right lung, rest of lungs clear	Hemoglobin, 80% White blood cells, 11,300 Red blood cells, 4,800,000 Polymorphonuclears, 81% Lymphocytes, 16%	16	Death, 12th day	Autopsy pulmonary edema lobular pneumonia (RLL)
22 F 73	378	Type IV	Lobar pneumonia (LVL)	Marked clouding on the right side extending from apex to fourth rib anteriorly, suggesting a pneumococcal consolidation conclusion, lobar pneumonia	Hemoglobin, 85% White blood cells, 16,400 Red blood cells, 4,500,000 Polymorphonuclears, 88% Lymphocytes, 11%	9	Recovery	
23 M 78	489	Type I, blood culture negative	Bronchial pneumonia (RLL)	No pulmonary infiltration or consolidation, numerous healed rib fractures		10	Recovery	

The subjects in the first year's experiment were observed for two years, with the exception of those who died from causes other than pneumonia and the fraction who were discharged and could not be followed up. Persons in the second year's experiment were observed for one year, with the same exceptions.

For the first group the value representing "years of life exposed" among the inoculated was 1,890 and among the controls 2,092. For the second group the number of "years of life exposed" among the inoculated was 708 and among the controls 684. Both groups being considered together, the incidence rate for the inoculated was 6.8 per thousand years of life and for the control group 37.4. From this it can be seen that the incidence rate for the noninoculated group was 4.25 times that for the inoculated.

The mortality rate calculated on the basis of a thousand years of life for the inoculated group was 5 and for the noninoculated 24.1, the rate for the noninoculated being almost 5 times higher than that for the inoculated group.

General and Local Reactions—Among all the immunized (1,750 persons) there were 86 reactions. Of these 51 had local reactions, showing redness of the skin around the point of injection, and 31 redness extending to the upper part of the arm. Four patients had, aside from the local reactions, general malaise and elevation of temperature to between 100 and 101.2 F, which subsided in all cases within twenty-four hours. The milder local reactions disappeared in ten to sixteen hours. No serious local or general reaction was noted.

Clinical Analysis of Cases of Pneumonia Among Inoculated Persons (Table 7)—There were 7 patients with lobar pneumonia, with 3 deaths, and 15 with bronchial pneumonia, with 10 deaths, in the inoculated group. At postmortem examination, 1 patient was found to have hypostatic pneumonia.

The type distribution in the two groups was as follows. In the inoculated group, 2 patients with type I, 1 with type II, 4 with type III, 1 with type IV and 1 with type XIX. In 2 cases nontypable diplococci and in 4 cases, long chains of streptococci were found, and the findings in 8 cases were bacteriologically irrelevant. In the control group there were 6 patients with type I, 3 with type II, 13 with type III, 2 with type IV, 3 with type VI, 3 with type VII, 1 with type IX, 1 with type XIV and 1 with type XIX. Nontypable pneumococci were found in cultures of material from 21 cases, long-chained streptococci in 22 cases and Koch's bacilli in 1 case, and in 25 cases the findings were bacteriologically irrelevant.

An analysis of the white blood cell counts (table 8) shows that there were 8 patients with between 10,000 and 15,000 leukocytes, 7 with less than 10,000, 4 with between 15,000 and 20,000 and 3 with between 25,000 and 30,000

The average duration of the disease was nine days. Pleural effusion was found in 2 cases. More than one lobe was involved in 4 cases. Bacteremia was found in 3 cases.

TABLE 8—*Summary of White Blood Counts of Patients with Pneumonia in Inoculated Group**

White Blood Count	No. of Cases	No. of Recoveries	No. of Deaths
Under 10,000	7	1	6
10,000 14,900	8	4	4
15,000 19,900	4	3	1
20,000 24,900	0	0	0
25,000 30,000	3	1	2

* Case 23 is unaccounted for

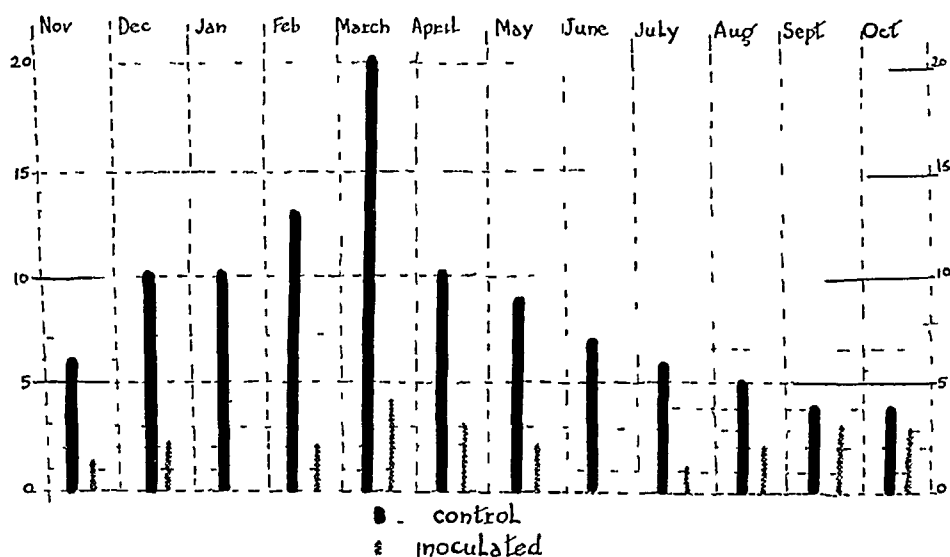


Chart showing month by month incidence of pneumonia among inoculated and control groups for two years

It may be concluded from the clinical analysis of the cases of pneumonia among the inoculated group that the disease in that group did not show any remarkable feature (as expressed by the course or duration of the disease, the complications or the case fatality rates) which would make it different from the usual clinical picture of old age pneumonia.

Duration of Immunity—The chart shows that the highest number of instances of pneumonia among the controls occurred, as is common on the eastern seaboard, in the month of March. There was an almost regular increase from November to March and a fairly regular decrease

from then on to the end of October. The same chart shows a different picture for the inoculated group. The incidence was almost even in November, January and February, with a relatively smaller seasonal increase in March. From here it was practically on an even level until August, when the height of the column reached about the same level as in March. In September and October it came down somewhat but it was relatively still higher than that for the noninoculated group. An analysis of the figures contained in the two tables (table 7, column 4, table 9) also shows that there were relatively more cases in the second than in the first half of the year. Although the number of cases was too small to warrant conclusions, there is an indication that the effect of the immunity was less pronounced in the last quarter than in the first three quarters of the year after immunization.

Isolated Epidemic in Two Wards—In one of the buildings (wards 51 and 52) an isolated epidemic of pneumonia occurred in the late spring

TABLE 9—*Interval Between Inoculation and Onset of Pneumonia*

Days From Inoculation to Onset of Pneumonia	No. of Cases
0-60	3
61-120	1
121-180	5
181-240	3
241-300	2
301-360	5
361-420	3
421-480	0
481-540	1

of 1939. There were 22 patients with pneumonia in a building where 154 people lived. Of these 154 persons 63 were inoculated in November 1938. There were among them 5 patients with pneumonia, 2 with lobar and 3 with bronchial pneumonia, and 2 of the patients died. Among the controls there were 17 with pneumonia, 8 with lobar and 9 with bronchial pneumonia, of these, 10 died. The type distribution in this epidemic was as follows. Among the inoculated, the infection in 1 patient was due to pneumococci of type II and in 1 to long-chained streptococci and in the rest the organisms could not be typed. Among the controls the organisms were in 2 pneumococci of type I, in 1 type II, in 1 type III, in 1 type XIX and in 3 pneumococci which could not be typed. Cultures in 2 cases showed streptococci, and in the rest the findings had no bacteriologic relevance. As can be seen, the data of this epidemic seem to confirm the findings of the main body of the experiments.

COMMENT

It is fairly well established that vaccines of killed or attenuated pneumococci have a prophylactic value. Not only animal experiments

but large scale inoculations done on human beings seem to substantiate this view ²⁰

The antigen used in these experiments is made from a fraction of the pneumococcus. It is a polysaccharide, containing nitrogen as well as carbohydrates and having no acetyl radical. Its chemical structure is not yet entirely known. No doubt the different preparations, sometimes even the different batches, are chemically not identical. But all contain dextrose and nitrogen. Felton and Kauffmann ²¹ stated the belief that proteins as well as lipoids and enzymes are primarily absent from the antigen. Goebel ²² and Heidelberger, Kendall and Scherp,⁸ assumed on the basis of analysis that it contains uronic acid and nitrogen. This is apparently near the final chemical structure, since with an artificial antigen chemically similar to the polysaccharides (azobenzylglycoside of cellobiuronic acid) Goebel succeeded, in experiments on mice, in conferring protection against type II, III and VIII pneumococci. In this way it was shown that not only the pneumococcus polysaccharides but their synthetic counterparts are capable of multiple antigenic action.

The data of the experiments reported here seem to substantiate these findings as far as the action of pneumococcus polysaccharides is concerned. The incidence and mortality rates of pneumonia were reduced not only for the types from which these substances were isolated but also for other types. It is true that the number of persons observed was relatively small (in the immunized and control groups together being 3,620), and since the period of observation was only two years, further observation is necessary to corroborate the data presented in this paper.

It seems obvious, however, that a group like the one used in these experiments is particularly suited for immunizations against pneumonia. As already pointed out, the high incidence, mortality and case fatality rates and the frequency of repeated attacks of pneumonia make active immunization among them a practical problem. Furthermore, since postoperative pneumonia is a dreaded complication in this age group, immunization with polysaccharide (if its prophylactic value can be definitely established) seems to be a procedure promising considerable reduction in the occurrence of pneumonia after surgical procedures.

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SUMMARY AND CONCLUSIONS

A report on active immunization with pneumococcic capsular polysaccharide against old age pneumonia in 1,750 subjects in a study conducted during the past two years is given

The data on the incidence, mortality and case fatality rates of the immunized are compared with those of 1,870 control patients

The following observations were made

1 While the incidence and mortality rates seem to be reduced among the inoculated, there is no appreciable effect on the case fatality rates

2 The course of pneumonia in the immunized group (as expressed by the length of the disease and the frequency of complications) was apparently not influenced by the inoculations

3 The prophylactic value seemed more pronounced in the first three quarters than in the last quarter of the year after immunization

FURTHER STUDIES ON HUMAN CARDIAC AND VOLUNTARY MUSCLE

POSSIBLE IMPLICATIONS OF CHANGES IN THE CREATINE, PHOSPHORUS
AND POTASSIUM CONTENT, WITH SPECIAL REFERENCE
TO HEART DISEASE

GEORGE H MANGUN, PH D

CHARLESTON, S C

AND

HERBERT S REICHLE, M D

AND

VICTOR C MYERS, PH D, D Sc

CLEVELAND

A number of studies have shown that the creatine concentration of cardiac and voluntary muscle is decreased in certain pathologic conditions. This work has been summarized in an earlier paper from this laboratory¹. The fundamental cause of the decrease in concentration of creatine in heart failure and other pathologic conditions has not been elucidated. However, certain facts are known that have an important bearing on this subject. Creatine is present in muscle largely in the form of phosphocreatine². That the exact amount present in this form cannot be determined by analysis is due to its rapid breakdown during manipulation of the sample. The best analyses suggest that about 75 to 80 per cent of the creatine present in voluntary muscle is in the form of phosphocreatine while in cardiac muscle the relative amount present in this form is much lower. Creatine can be readily washed out of

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From the Departments of Biochemistry and Pathology (City Hospital Division), School of Medicine, Western Reserve University

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The chemical data in this paper are taken from a dissertation submitted by George H Mangun to the Graduate School of Western Reserve University, June 1938, in partial fulfilment of the requirements for the degree of Doctor of Philosophy

1 Linegar, C R, Frost, T T, and Myers, V C. Variation in Creatine Content of Human Cardiac and Voluntary Muscle at Autopsy, *Arch Int Med* **61** 430 (March) 1938

2 Fiske, C H, and Subbarow, Y. Phosphocreatine, *J Biol Chem* **81** 629 1929

cardiac muscle by perfusion³ In skeletal muscle the rate at which creatine⁴ diffuses out has been shown to be greater in fatigued than in resting muscle, probably because of a greater dissociation of phosphocreatine That the retention of creatine by muscles is not due to impermeability of the cells is suggested by the fact that administered creatine can be taken up by muscle⁵ It has been shown that the administration of creatine⁶ causes a decrease in the amount of phosphorus in the urine, evidence that this creatine is actually stored in the tissues as phosphocreatine This evidence, together with a large body of other facts, suggests that variations in the creatine content of cardiac and voluntary muscle are, under conditions of equilibrium, reflections of variations in the metabolism of phosphocreatine

Phosphocreatine is strongly acid in character and at the p_H commonly assigned to the interior of muscle cells would be largely present in the dibasic form Since potassium is the chief base of the cells, it appears logical to assume that phosphocreatine exists in the living cells as dipotassium phosphocreatine⁷ One might, therefore, anticipate a parallel decrease in creatine, phosphorus and potassium if the loss of creatine is attributed to a breakdown of phosphocreatine or failure of its resynthesis Calhoun, Cullen, Clark and Harrison⁸ have shown that the total phosphorus and potassium are decreased in the hearts of persons dying of congestive heart failure, an observation in accord with the aforementioned hypothesis

In the present study, creatine, phosphorus and potassium determinations were carried out on muscle from the left and right ventricles of the heart and on skeletal muscle (pectoralis major) to establish what relation, if any, existed among the losses of these muscle constituents

3 (a) Burns, W, and Cruickshank, E W H Changes in Creatine, Phosphagen and Adenylpyrophosphate in Relation to the Gaseous Metabolism of the Heart, *J Physiol* **91** 314, 1937 (b) Linegar, Frost and Myers¹

4 Eggleton, P The Diffusion of Creatine and Urea Through Muscle, *J Physiol* **70** 294, 1930 Tiegs, O W Function of Creatine in Muscular Contraction, *Australian J Exper Biol & M Sc* **2** 1, 1925

5 Myers, V C, and Fine, M S The Influence of the Administration of Creatine and Creatinine on the Creatine Content of Muscle, *J Biol Chem* **16** 169, 1913

6 Brown, M, and Imbrie, C G The Influence of Creatine on the Excretion of Phosphate by the Kidney, *J Physiol* **71** 222, 1931

7 Myers, V C, and Mangun, G H Comparative Studies on Creatine, Phosphorus and Potassium in Various Muscle Tissues, *J Biol Chem* **132** 701, 1940

8 Calhoun, J A, Cullen, G E, Clark, G, and Harrison, T R Studies in Congestive Heart Failure VIII The Effect of the Administration of Dibasic Potassium Phosphate on the Potassium Content of Certain Tissues, *J Clin Investigation* **9** 693, 1931

METHOD

Samples were obtained from the left and right ventricles and the pectoralis major muscle of human beings during autopsy, according to the method described by Seecof, Linegar and Myers⁹ The analyses were carried out on a single sample as described in another paper,¹⁰ dealing with normal tissue, the creatine being determined as described in earlier papers in this series,¹¹ the phosphorus by the method of Fiske and Subbarow¹² and the potassium by the permanganate titration method of Kramer and Tisdall¹³ Care was taken to avoid possible postmortem changes, and with 4 exceptions all samples were taken within twenty-four hours post mortem

Determinations were carried out on muscle from the left and right ventricles of 95 human beings For 61 of them, analyses were also made of voluntary muscle (pectoralis major) Thirteen of the 61 were victims of sudden death, and the samples of their muscles were obtained at the Cuyahoga County Morgue, the data on these subjects were discussed in a separate paper¹⁰ The remaining subjects have been classified in groups according to the major diagnoses or included in the miscellaneous group

RESULTS

The average results obtained for the 13 normal persons and the 82 with a pathologic condition are summarized in table 1 The difference between the left and the right ventricle was very nearly the same in the normal subjects and in those with a pathologic condition The probable source of this difference between the two ventricles will be discussed in more detail in a later section, but at this point it is well to establish the normal relationships The average difference between the left and the right ventricle was 22.1, 20.3 and 23.2 per cent for creatine, phosphorus and potassium respectively, the left ventricle being used as the standard of reference The finding of essentially the same percentage of difference between the left and the right ventricle for each constituent suggests that muscle dilution may be the principal factor responsible for the differences between the two ventricles

In all but 2 instances, the concentrations were higher in the left ventricle than in the right Seecof, Linegar and Myers⁹ found a higher concentration of creatine in the left ventricle in every instance in a series of 108 human hearts, except in 1 newborn infant

Myocardial Insufficiency—Included in this group were only those patients whose condition was clinically diagnosed as myocardial insuf-

9 Seecof, D. P., Linegar, C. R., and Myers, V. C. The Difference in Creatine Concentration of the Left and Right Ventricular Cardiac Muscles, *Arch Int Med* **53** 574 (April) 1934

10 Mangun, G. H., and Myers, V. C. Normal Creatine, Phosphorus and Potassium Content of Human Cardiac and Voluntary Muscle, *J Biol Chem* **135** 411 (Sept.) 1940

11 Linegar, Frost and Myers¹ Seecof, Linegar and Myers⁹

12 Fiske, C. H., and Subbarow, Y. The Colorimetric Determination of Phosphorus, *J Biol Chem* **66** 375, 1925

13 Kramer, B., and Tisdall, F. S. A Clinical Method for the Determination of Small Amounts of Potassium in Serum, *J Biol Chem* **46** 339, 1921

iciency and who showed evidence of progressive decompensation with hyperemia of the internal organs and edema of the extremities. Patients with less distinct signs of myocardial insufficiency were placed with the group having miscellaneous cardiac involvements. All patients with

TABLE 1—*Summary of Observations on Creatine, Phosphorus and Potassium Content of Cardiac and Voluntary Muscle in 13 Normal and 82 Diseased Persons (Mg/100 Gm of Wet Tissue)*

		Creatine		Phosphorus		Potassium	
		Normal	Diseased	Normal	Diseased	Normal	Diseased
Left ventricle	Average	203	199	194	187	285	267
	Maximum	218	330	204	235	305	332
	Minimum	186	99	180	108	251	170
Right ventricle	Average	165	155	160	149	219	205
	Maximum	184	238	187	227	242	275
	Minimum	154	70	140	105	189	114
Pectoralis major *	Average	443	405	201	192	328	314
	Maximum	462	538	216	245	346	415
	Minimum	442	212	195	113	311	169

* Thirteen normal persons and 48 with some pathologic condition

TABLE 2—*Myocardial Insufficiency (Values Calculated per Hundred Grams of Fresh Tissue)*

Number	Age	Sex	Hours Post Mortem	Heart Weight, Gm	Left Ventricle			Right Ventricle			Voluntary Muscle		
					Creatine, Mg	Phosphorus, Mg	Potassium, Mg	Creatine, Mg	Phosphorus, Mg	Potassium, Mg	Creatine, Mg	Phosphorus, Mg	Potassium, Mg
72	42	F	6	350	170	177	241	121	141	190	371	182	276
60	67	F	4	400	169	173	245	121	135	182	344	181	264
43	60	F	55	425	167	175	223	131	152	164	321	167	245
31	65	F	2	375	165	169	260	113	144	196			
19	68	M	7	600	161	171	185	110	132	152			
37	39	M		675	159	197	206	116	125	153	338	138	265
67	52	M	12	475	155	180	233	137	144	189	343	190	256
6	53	M	9	550	154	108	225	147	107	192			
75	58	M	2	525	148	170	236	126	139	189	357	190	247
15	58	M	6	550	145	152	244	135	141	134			
36	30	F		825	143	172	222	117	114	173			
11	59	M	54	525	143	166	293	91	105	195			
13	39	M	5	750	131	177	174	136	187	184	278	144	336
39	53	M	9	800	128	190	251	70	135	179	333	194	285
4	56	M	78	575	126	147	170	88	117	145			
45	42	M	5	600	120	180	290	72	137	201	305	195	350
41	43	M	4	450	99	171	244	78	138	218			
Average					146	169	232	112	135	178	349	177	237

clinical proof of nitrogen retention were grouped together as having uremia with heart failure. No patients were included here who showed anatomic evidence of severe renal disease, even though there was no clinical proof to substantiate the anatomic findings. Such patients were included in the group with miscellaneous cardiac involvements.

It becomes evident from an inspection of table 2 that the concentrations of creatine, phosphorus and potassium were decreased in both

ventricles of the heart and in the voluntary muscle. In every case the creatine content of the left ventricle was below the normal level. The concentration of phosphorus was likewise lowered, but to a lesser degree in all but 2 cases. The potassium decreased in all but 2 cases, the average percentage of decrease being somewhat more than that of phosphorus and less than that of creatine. Similar findings were recorded for the right ventricle. In every case the creatine concentration of the voluntary muscle was below the normal level, that of phosphorus and that of potassium were more variable, but the average values were definitely lowered. After the changes were analyzed more closely, it was believed to be more to the point to consider that portion of each constituent lost, rather than changes occurring in the total amount present in normal muscle. This assumption arose from the fact that

TABLE 3—*Molecular Relationships Among the Losses of Creatine, Phosphorus and Potassium (Millimols per Kilogram of Wet Tissue)*

	Left Ventricle			Right Ventricle		
	Creatine	Phosphorus	Potassium	Creatine	Phosphorus	Potassium
Average of 91 patients	15.1	60.5	68.8	11.8	48.3	54.2
Congestive heart failure	11.1	54.5	59.4	8.5	43.5	46.5
Decrease, millimols	4.0	6.0	9.4	3.3	4.8	7.7
Decrease, percentage	26.6	10.1	13.7	28.0	10.0	14.2
Mols required for loss of dipotassium phosphocreatine	4.0	4.0	8.0	3.3	3.3	6.6
Additional P and K lost		2.0	1.4		1.8	1.1

all of the phosphorus and potassium present is not directly concerned with creatine. Therefore, if the changes observed were primarily due to variations in the creatine-phosphocreatine mechanism, only that part of the phosphorus and potassium directly associated with the creatine might be expected to vary. On the other hand, if the observed decreases were due chiefly to dilution of the active muscle tissue with water, fat or connective tissue, one might anticipate that the whole of the creatine, phosphorus and potassium would be affected. The net result would be that a decrease of 10 per cent, for example, in the creatine would be accompanied by a decrease of 10 per cent in the phosphorus and potassium.

Table 3 shows the changes that occurred in this group in terms of percentage decrease in the three constituents and in terms of loss in millimols per kilogram. From these data it is apparent that tissue dilution was not the important factor involved, since there was no correlation between the percentage decreases of the three constituents in either ventricle.

If one assumed a loss of the constituents of dipotassium phosphocreatine, using the loss of 4 mols of creatine as the standard of reference, one would expect a loss of 4 mols of phosphorus and 8 mols of potassium. The actual loss of the latter two exceeded that of creatine. This fact is suggestive of a loss of adenylypyrophosphate, in accordance with the findings of Burns and Cruickshank^{3a} and others that this compound may break down under a variety of experimental conditions.

TABLE 4—*Miscellaneous Cardiac Involvements (Values Calculated per Hundred Grams of Fresh Tissue)*

Number	Age	Sex	Hours Post Mortem	Heart Weight, Gm	Left Ventricle			Right Ventricle			Voluntary Muscle		
					Creatine, Mg	Phosphorus, Mg	Potassium, Mg	Creatine, Mg	Phosphorus, Mg	Potassium, Mg	Creatine, Mg	Phosphorus, Mg	Potassium, Mg
12	55	M	13	625	294	163	240	132	122	210			
53	55	F	10	325	253	197	286	192	154	155	343	192	284
55	77	F	2	450	252	168	282	198	143	190	353	156	237
51	32	M	3	750	236	175	284	194	143	184	405	182	304
1	35	F	1	325	233	173	256	195	158	230			
54	53	M	4	700	213	181	285	169	152	212	339	178	285
40	56	M	7	350	206	199	292	189	134	119			
59	42	F	4	375	202	197	264	148	147	207	421	198	314
23	67	M	9	475	195	210	307	160	202	243			
38	50	M	6	485	194	186	260	119	119	171			
32	49	M	9	400	192	197	250	97	93	134	480	206	270
56	86	F	2	175	191	182	273	136	141	191			
13	45	M	2	375	190	189	332	168	142	236			
16	73	F	6	150	185	166	187	119	114	137			
66	58	F	9	500	186	188	251	142	148	197	347	182	276
63	62	M	7	525	177	178	254	139	147	193	394	191	307
44	58	M	5	425	176	197	292	105	155	165	388	226	322
26	55	M	16	600	173	194	251	154	180	239			
69	61	F	7	475	165	179	234	126	137	189	374	186	294
14	36	M	4	375	164	162	250	147	148	223			
28	64	F	3	350	163	210	200	119	153	127	415	184	197
50	73	M	5	500	163	161	217	125	136	100	212*	113*	169*
22	62	F	11	650	157	212	285	144	182	275			
34	52	F	3	500	141	185	229	113	138	197			
Average					195	185	261	147	145	190	384	188	283

* This sample of muscle contained a large amount of fat, the values were not used in calculating the averages.

It is improbable that any extensive changes occur in compounds of phosphorus other than phosphocreatine and adenylypyrophosphate. Phosphate esters are present in too small quantities to account for the phosphorus decreases observed in these human hearts. Inorganic phosphorus would be more likely to increase than to decrease because of the liberation of phosphorus from phosphocreatine and adenylypyrophosphate. As the heart is stimulated to greater work and as its nutritional condition becomes poorer, fatigue and anoxemia may become progressively greater until the heart is no longer able to resynthesize phosphocreatine and adenylypyrophosphate as fast as they are broken down.

Miscellaneous Cardiac Involvements—This group included all patients who showed significant changes in the heart but did not clinically manifest appreciable cardiac insufficiency.

It is worthy of note that of the first 6 patients in this group, 5 showed anatomic evidences of renal involvement (patients 2, 53, 55, 51 and 54) However, in the absence of clinical evidence of retention, they were excluded from that classification The condition in patient 54 was also clinically diagnosed as cardiac failure, but the patient was excluded from this classification because of the possible nitrogen retention

In 4 instances (patients 2, 40, 38 and 44) of right-sided heart failure (cor pulmonale), the left ventricle averaged 217, 186 and 271 mg of creatine, phosphorus and potassium and the right ventricle 136, 132 and 166 mg respectively in each 100 Gm On the basis of the chemical data, it is appaent that when the left ventricle fails, the right ventricle also

TABLE 5—Uremia Without Heart Failure (Values Calculated per Hundred Grams of Fresh Tissue)

Number	Age	Sex	Hours Post Mortem	Heart Weight, Gm	Left Ventricle			Right Ventricle			Voluntary Muscle		
					Creatine, Mg	Phosphorus, Mg	Potassium, Mg	Creatine, Mg	Phosphorus, Mg	Potassium, Mg	Creatine, Mg	Phosphorus, Mg	Potassium, Mg
83	37	M	3	340	330	218	310	165	143		502	245	367
47	37	M	4	400	272	172	289	220	165	194	431	244	390
52	43	M	6	275	266	213	317	238	176	241	487	202	352
35	50	F	12	520	265	217	331	134	144	197	407	216	314
48	56	M	3	350	248	195	252	207	126	204	421	208	415
70	54	F	11	425	247	211	302	186	164	241	468	221	337
30	78	M	2	450	246	184	234	135	123	198	538	195	338
78	60	M	10	275	215	214	257	185	153	169	438	192	329
12	4½	M	4	125	214	188	271	174	165	204			
49	47	M	2	375	212	189	266	202	181	215	495	187	295
71	40	M	5	350	194	190	271	121	138	181	418	207	331
Average					246	199	286	182	153	205	461	212	347

fails, but the right ventricle may show chemical evidence of failure without similar changes occurring in the left ventricle, as is evident from this small series of 4 cases

In 1 case of coronary thrombosis (patient 13), in which the sample was taken from an area that was not infarcted, the values for all three constituents were within the normal range In patient 56 with brown atrophy of the heart, the values were slightly below normal with the exception of that for potassium in the left ventricle

Uremia without Heart Failure—Table 5 lists the patients who were classified as having uremia without heart failure Nearly all of these patients' hearts were diseased or hypertrophic to some extent, but the clinical signs of heart failure were either absent or moderate Those patients with cardiac decompensation have been grouped together as patients with uremia with heart failure This classification was based on the earlier findings of Linegar, Frost and Myers ¹

The creatine content of both ventricles and that of the voluntary muscle were distinctly higher than in the 13 normal hearts. In this group the creatine content of the left ventricle was higher than in any of the normal hearts in 7 of 11 patients; that of the right ventricle was above normal range in 7 patients, and that of voluntary muscle was above normal range in 5 of 10 patients.

Although the average phosphorus values for both ventricles were well within the normal range, it should be noted that 5 of the values for the left ventricle were definitely above the normal limits, while those for the right ventricle were lower and more variable.

The potassium content of the three tissues corresponded closely with that of phosphorus, although there were some individual variations. The average potassium content of the left ventricle was in the upper normal range and that of the right ventricle was somewhat lower. The potassium content of voluntary muscle appeared to be definitely higher than the normal value. Four of the potassium values were above the normal limits and four were near the upper normal level.

The most outstanding fact about this group was the relatively high values for voluntary muscle. In all other pathologic conditions that we encountered in this series the average values were well below the average of the normal group. This was in marked contrast to the situation in cardiac muscle, in which creatine, phosphorus and potassium were undiminished unless cardiac disease was evident and often appeared to be augmented. This difference in the behavior of the two types of muscle may be of considerable physiologic importance. By liberation of these substances from muscle tissue in other parts of the body the functional capacity of the heart may conceivably be increased during emergencies.

Uremia with Heart Failure—In this group of patients the results were much more variable than in the group of those who were classified as having uremia without heart failure. In general the values for all three constituents were essentially normal for the group, with perhaps a slight elevation in the creatine content and the potassium content of voluntary muscle. One can only say that in cases of uremia with heart failure high, low or normal values may be encountered in contrast to the consistently high values in cases of uremia without heart failure.

A comparison of the findings for patients with uremia alone and for patients with heart failure alone leads to the conclusion that here there are two factors with opposite influence on the level of creatine, phosphorus and potassium in cardiac muscle.

Presumably the predominant factor determines the net result, but our present knowledge of the factors involved does not permit any quantitative evaluation of them. It may be suggested that in retention creatine, phosphorus and potassium may be retained in excessive amounts.

in voluntary and cardiac muscle only when the nutritional condition, and possibly other unknown factors, is favorable for such a storage. This further suggests that the retention by the muscles of creatine, and also of phosphorus and potassium, is dependent on such a process as the formation of phosphocreatine. In the case of phosphorus and potassium there is the additional possibility that other organic phosphorus compounds may also vary. That such variations do occur is borne out by the lack of correlation in many patients between the values for creatine and those for phosphorus and potassium.

It is quite conceivable that the retention of creatinine (creatinine \rightleftharpoons creatine), and also of phosphorus and potassium, in advanced renal disease may have some effect on the course of heart failure. By

TABLE 6—*Uremia with Heart Failure (Values Calculated per Hundred Grams of Fresh Tissue)*

Number	Age	Sex	Hours Post Mortem	Heart Weight, Gm	Left Ventricle			Right Ventricle			Voluntary Muscle		
					Creatine, Mg	Phosphorus, Mg	Potassium, Mg	Creatine, Mg	Phosphorus, Mg	Potassium, Mg	Creatine, Mg	Phosphorus, Mg	Potassium, Mg
80	41	M	12	600	246	202	282	186	151		445	183	276
27	57	M	4	575	240	209	301	216	203	272			
29	49	M	3	625	242	235	295	232	172	248	450	220	286
58	33	M	12	425	227	183	275	182	125	226	450	214	400
57	49	M	10	500	220	173	305	173	161	242	393	160	359
68	47	F	6	550	196	184	258	147	142	191	409	190	311
46	69	F	8	300	192	158	236	172	130	186	386	199	401
76	56	M	10	600	185	202	231	144	147		507	219	335
33	66	M	3	550	181	178	218	156	144	189	488	209	362
Average					214	192	267	179	153	222	441	199	341

reason of their retention in the blood it is possible that, since they are available in greater amounts than normal, they would promote the resynthesis of phosphocreatine and thus ward off, to some extent at least, the depletion of phosphocreatine and its constituents which ordinarily occurs in the failing heart. At any rate the values for creatine, phosphorus and potassium tend to be definitely higher in patients with uremia without heart failure than in patients with uremia with heart failure, and this is particularly evident in the left ventricle.

Miscellaneous Pathologic Conditions—Data on patients whose conditions did not fall into one of the major groups are shown in table 7. The left and right ventricles of patients in this group are notable in that the concentrations of creatine, phosphorus and potassium were almost identical or slightly higher than those of the 13 normal persons, while in voluntary muscle the values were appreciably less.

It will be observed that the potassium content of the right ventricle was higher in this group than in the normal group, 231 mg. as compared

with 219 mg. This difference was due probably to a loss of potassium that occurred in some of the normal hearts during the time between autopsy and trimming of the sample. The value of 231 mg. agrees fairly well with the observations of Wilkins and Cullen¹⁴ on the right ventricle.

A comparison of the variability of the values in the group of normal persons and in the group of patients with miscellaneous pathologic conditions reveals a distinct contrast. In the former group the difference between the highest and lowest creatine concentrations of the left ventricle was 32 mg., as compared with 100 mg. in the latter group,

TABLE 7—Miscellaneous Pathologic Conditions (Values Calculated per Hundred Grams of Fresh Tissue)

Number	Age	Sex	Hours Post Mortem	Heart Weight, Gm	Left Ventricle			Right Ventricle			Voluntary Muscle		
					Creatine, Mg	Phosphorus, Mg	Potassium, Mg	Creatine, Mg	Phosphorus, Mg	Potassium, Mg	Creatine, Mg	Phosphorus, Mg	Potassium, Mg
21	69	M	4	275	270	188	322	178	145	216			
82	43	M	6	225	247	202	261	159	137		369	186	280
	18	F	5	50	244	202	295	188	164	240			
18	67	F	4	275	238	203	322	195	158	243			
25	37	M	50	300	238	180	320	156	139	235			
8	58	F	7	225	236	178	275	184	158	232			
9	54	M	14	250	232	197	283	194	172	264			
61	65	M	5	300	221	197	286	164	159	219	440	204	347
17	50	M	12	350	220	209	324	212	164	260			
5	64	M	2	250	216	175	285	148	158	240			
62	47	M	4	325	216	192	286	120	141	194	358	172	271
20	20	F	2	200	206	211	314	169	175	264			
24	44	F	10	230	205	220	298	220	227	264			
74		M	14		205	192	261	164	157	198	424	204	340
10	50	F	9	210	205	196	310	156	172	224			
81	49	M	5	400	204	214	288	125	146		376	190	283
64	47	M	3	325	193	190	269	147	153	201	382	196	297
73		F	10		191	187	255	151	154	197	415	199	299
84	36	M	3	280	186	191	206	153	154		431	194	307
65	39	F	14	350	181	186	243	134	145	194	399	187	305
7	1	M	5	50	170	218	301	154	176	271			
Average					218	197	286	166	160	231	399	192	303

the phosphorus varied 24 mg. in the former and 45 mg. in the latter, and the potassium varied 54 mg. in the former and 118 mg. in the latter. Similar variations occurred in the right ventricle and in voluntary muscle. The greater degree of variations in the latter group indicated that there were appreciable changes in this group well outside the limits of experimental error.

It would, of course, be of advantage to subdivide the group of patients with miscellaneous conditions further, if by so doing one could differentiate those patients with high values and those with low

14 Wilkins, W. E., and Cullen, G. E. Electrolytes in Human Tissues. III. A Comparison of Normal Hearts with Hearts Showing Congestive Heart Failure, *J. Clin. Investigation* **12**: 1063, 1933. Calhoun, Cullen, Clark and Harrison.⁸

values Seven patients may be classified as having acute infections (patients 82, 3, 8, 9, 20, 24 and 10) Five of these patients died of acute peritonitis and the remaining 2 of septicemia The creatine, phosphorus and potassium in the left ventricle averaged 224, 201 and 291 mg, and in the right ventricle 181, 172 and 248 mg respectively No data are available on voluntary muscle In general, these figures are somewhat above the average of the group of normal persons

Patient 18, who showed definitely elevated values, should perhaps be classified with the group of patients with nitrogen retention, although there were no chemical data on the blood to substantiate this assumption

In 3 patients with diabetes mellitus (patients 81, 65 and 62) the creatine, phosphorus and potassium averaged 200, 197 and 272 mg in the left ventricle, 126, 144 and 194 mg in the right ventricle, and 378, 183 and 286 mg in voluntary muscle respectively This was a definite decrease in the values for voluntary muscle and for the right ventricle, with practically normal values for the left ventricle Another patient with diabetes mellitus (patient 83), whose case is not tabulated here, was included among the patients with uremia, because of nitrogen retention

No explanation can be given for the elevated creatine values found in case 21

COMMENT

The changes in the concentration of creatine, phosphorus and potassium in cardiac muscle associated with cardiac decompensation appear to be the most significant results of this study It is evident that the relative losses of creatine, phosphorus and potassium are of such a magnitude as one might expect if these changes resulted chiefly from a breakdown of phosphocreatine The argument that a decrease in the relative amount of active muscle, as a result of edema, infiltration of fat and fibrosis, is the cause of the decreased concentrations of creatine, phosphorus and potassium does not fit the experimental data Analyses in which fat and water were also determined have shown that values calculated on a fresh weight basis agreed better with other findings than those calculated on a dry weight basis, unless the fat content was also included The fat content of the heart was found to vary greatly, but was usually higher in the right ventricle than in the left ventricle

The analyses reported here have confirmed the decrease in phosphorus and potassium observed by the investigators at Vanderbilt Medical School¹⁴ The decrease in total phosphorus has been supplemented by a smaller series of determinations of acid-soluble phosphorus No significant variations were found to occur in the acid-insoluble fraction, but the acid-soluble phosphorus varied to a greater extent, and with 1 exception, in a patient with diabetes mellitus, fol-

lowed closely the creatine concentration. It would therefore appear that the variations encountered in phosphorus were the result of changes in the concentration of acid-soluble phosphorus. Since the completion of this study Decherd and Blum¹⁵ have reported analyses of the left ventricle of the human heart in 36 cases in which there was heart failure and in 33 cases in which there was no heart failure. They found a definite decrease in the acid-soluble phosphorus but no change in the acid-insoluble phosphorus.

Burns and Cruickshank^{3a} recently investigated the effects of asphyxia and fatigue on the mammalian heart. They found that in asphyxia there was a loss of phosphocreatine and of adenylypyrophosphate, which in complete asphyxia was approximately 80 and 60 per cent respectively. With fatigue in the presence of oxygen they found the situation reversed, with an approximate loss of 25 per cent of the phosphocreatine and 50 per cent of the adenylypyrophosphate. These findings are in substantial agreement with the results of our study. Since tissue anoxia and fatigue are the two conditions most probably associated with cardiac decompensation, these findings fit satisfactorily into the hypothesis that the loss of phosphorus and potassium results from the decomposition of the dipotassium salt of phosphocreatine and other organic phosphates.

A study of the phosphorus compounds of the dog's heart in aortic insufficiency has recently been completed by Mangun and Roberts¹⁶. In the late stages of insufficiency in 2 dogs a marked loss of adenylypyrophosphate, as well as phosphocreatine, was observed, amounting to 40 per cent of the total pyrophosphate and 20 per cent of the phosphocreatine normally present. Essentially no change occurred in the inorganic phosphorus and the ester phosphorus.

The most recent studies¹⁷ in our laboratories on the human heart have included the estimation of the total extractive purines. Assuming that the purine determined is present in the living tissue largely in the form of adenylypyrophosphate, these studies indicate that adenylypyrophosphate is present in about half the molecular concentration of the phosphocreatine. Determinations of creatine, extractive purine nitrogen and total acid-soluble phosphorus have been made on 24 human hearts. In 6 instances of myocardial failure the creatine was decreased about 33 per cent, extractive purines about 15 per cent and phosphorus about 14 per cent below the average of the series. Creatine, extractive oxy-

15 Decherd, C. M., and Blum, J. E. Phosphorus Fractions in Human Heart Muscle, *Proc Soc Exper Biol & Med* **38** 341, 1938.

16 Mangun, G. H., and Roberts, J. T. The Relationship of Phosphorus to Creatine in Cardiac Muscle, read at the Meeting of the Division of Biological Chemistry of the American Chemical Society, Boston, September 1939.

17 Mangun, G. H., and Myers, V. C. Purine Content of Human Cardiac and Voluntary Muscle, *J Biol Chem* **133** 1411, 1940.

purine nitrogen and total acid-soluble phosphorus averaged 205, 35.5 and 106 mg per hundred grams respectively in the left ventricle of the 24 hearts and 161, 30.0 and 91 mg in the 6 hearts of patients with myocardial failure. While the change in purine content is not as great as that in creatine, still it does indicate that there may be a considerable loss of adenylypyrophosphate from the heart.

Whether the chemical changes observed in myocardial failure, viz., the fall in creatine, phosphorus, potassium and purines (adenylypyrophosphate) are contributory to or merely associated with this condition obviously cannot be determined on the basis of the data available. However, if the present theories regarding the energetics of muscle are correct, the fall in the content of these constituents must reduce the capacity for work.

SUMMARY

Creatine, phosphorus and potassium determinations have been carried out on the samples of muscle from the left and right ventricles of the hearts obtained at autopsy from human beings with pathologic conditions. In 48 instances analyses were also carried out on voluntary muscle.

The content of creatine, phosphorus and potassium in the left and right ventricles and in voluntary muscle averaged about 5 per cent less than in samples from 13 normal persons and varied considerably more.

In 17 patients with congestive heart failure, the creatine, phosphorus and potassium concentrations of both ventricles and of voluntary muscle were consistently decreased. The percentage decrease was greatest for creatine and least for phosphorus, while potassium occupied an intermediate position.

The average figures obtained for persons with heart failure showed a loss of 40 mols of creatine, 60 mols of phosphorus and 94 mols of potassium per kilogram. It is suggested that this loss is due primarily to a breakdown of dipotassium phosphocreatine with a subsequent loss of its components.

In uremia the creatine, phosphorus and potassium contents of voluntary muscle were found to be somewhat higher than the average values, 50 per cent of the values being higher than the normal range. Values for cardiac muscle were also relatively high. The increase in the creatine content of voluntary and cardiac muscle in uremia finds probable explanation in the retention of creatinine and the equilibrium which exists between creatinine and creatine. The changes in the phosphorus and potassium are probably related to the creatine changes.

The creatine, phosphorus and potassium values tended to be decreased in voluntary muscle in all conditions not associated with nitrogen retention, with the possible exception of fever and emaciation. Values in cardiac muscle, on the contrary, were usually normal or slightly elevated, unless heart disease was evident.

HEMOCHROMATOSIS

REPORT OF A CASE

A CANTAROW, M D

AND

CARL J BUCHER, M D

PHILADELPHIA

The following case is reported primarily because of (a) the absence of glycosuria and of significant decrease in dextrose tolerance in spite of the unusual quantity of iron in the liver and pancreas, (b) the absence of iron-containing pigment in the apparently characteristically pigmented skin, (c) the unusual complication of cutaneous xanthomatosis with hypercholesteremia in the absence of diabetes, (d) the antemortem demonstration of deficiency in adrenal cortical and androgenic hormones and (e) the unusual cause of death

REPORT OF CASE

History—S S, a white Polish coal miner aged 45, was admitted to the service of Dr H A Reimann, Jefferson Medical College Hospital, on Sept 9, 1938, with the following complaints (1) blue-gray discoloration of the skin (four years' duration), (2) intense itching (four years), (3) abdominal enlargement (three years) and (4) swelling of the legs (nine months)

The family history and past medical history had no bearing on the present condition

Present Illness—In July 1934 the patient first noted slight grayish blue pigmentation on the face and arms, which spread to the trunk and legs, increasing in intensity during the next two months. It varied little in intensity from August to the time of admission. Generalized itching began at the same time and persisted. Studies at another hospital on June 6, 1934 revealed the following conditions: deep slate color of the skin, with jaundice and enlargement of the liver and the spleen, icterus index, 100, Wassermann reaction, negative, basal metabolic rate, normal, and gastrointestinal roentgenogram, normal. The diagnosis on discharge was Banti's disease. Reexamination at the same hospital on Dec 2, 1937 revealed, in addition to the aforementioned changes, rarefaction of the long bones, and it was noted on bronchoscopic examination that the mucous membrane of the pharynx, larynx and trachea was of essentially the same color as the skin. The diagnosis of biliary cirrhosis was made at that time. Abdominal enlargement was first noted by the patient in June 1935 and increased steadily. The appetite was poor, and there was constipation. There was a gradual loss of strength and energy. No sexual desire had been felt for the previous six years.

Physical Examination—The skin over the entire body was deep slate blue with a bronze tint. The blue was most pronounced on the face and arms, and the pigmentation was most intense on the external genitalia. There was no abnormal pigmentation of the conjunctivas or of the lingual or buccal mucous membranes.

From the Department of Medicine and the Laboratories of Biochemistry and Pathology, Jefferson Medical College Hospital

The lips were deeply pigmented (blue bronze), as was the mucous membrane of the lower part of the rectum. The scleras were yellow.

There were many xanthomatous lesions distributed over both upper eyelids, the flexor and extensor surfaces of the elbows, the palm of the right hand, the anterior and posterior axillary folds and the back of the chest. These lesions were slightly raised and dull lemon yellow and varied in longest diameter from about 2 to 10 mm. There were scratch marks over the entire surface of the body.

The hair was of fine texture and not abundant but had normal distribution. There was a complete but reducible left inguinal hernia. Both testes were small and of flabby consistency, the left being almost impalpable. The prostate was small.

The heart appeared normal. The lungs showed signs suggesting anthracosis of moderate degree. The abdomen was markedly distended, particularly on the left side. The liver extended 5 cm below the costal margin in the right midclavicular line. The edge was hard and sharp and the surface was smooth and not tender. The spleen was smooth and hard and extended 14 cm below the costal margin. There was no evidence of ascites. The fingers showed moderate clubbing, and there was bilateral Dupuytren's contracture. The temperature was 98 F, the pulse rate, 85, the respiratory rate, 20, and the blood pressure, 100 systolic and 60 diastolic. There was no edema of the extremities, and the peripheral vessels were not unduly thickened. The eyegrounds were normal, showing no abnormal pigmentation.

Roentgen Ray Examination—Roentgenograms showed a moderate degree of anthracosis of the lungs, diffuse demineralization of the entire skeleton, enlargement of the liver and spleen, widening of the duodenal loop and deformity of the duodenal cap.

Electrocardiographic Examination—An electrocardiogram taken on Sept 15, 1938 was normal.

Histologic Examination (Skin)—On September 23 microscopic studies showed an excess of melanin pigment in the normal situation. There was no evidence of iron-containing pigment. A section through a xanthomatous area showed characteristic cells of that type of lesion.

Laboratory Studies—Many of the significant results of laboratory tests are presented in tables 1 and 2. Additional findings were as follows:

Urine (several examinations). One plus reaction for albumin and 2 plus reaction for bilirubin were obtained, but there was no dextrose, melanin, hemosiderin-containing cells or porphyrins. Volume 1,000 to 2,000 cc daily. Fluid intake 1,500 to 2,500 cc daily.

Bile and Feces. Bile obtained by duodenal drainage showed no significant abnormality. The feces contained a slight excess of neutral fat and fatty acids but were otherwise normal.

Gastric Analysis (Histamine). Free hydrochloric acid rose to a maximum of 6 and total acid to a maximum of 20 in forty-five minutes.

A sternal puncture on September 15 (Dr Tocantins) showed no abnormalities.

A splenic puncture on September 15 (Dr Tocantins) showed no abnormalities. No xanthoma cells were seen.

The basal metabolic rate on September 15 was +16 per cent.

Course—The patient left the hospital on November 4 and was readmitted, with the same complaints and with increased weakness, on Jan 13, 1939. The results of physical examination were essentially the same as previously except that the liver (6 cm below the costal margin) and the spleen (16 cm below the costal margin) had apparently increased in size. The bronze tint of the skin was distinctly more pronounced, and there was slight pretibial edema.

Peritoneoscopic examination was performed on January 17 (Dr K Fry) The liver was enlarged and appeared to be of a gray-bronze color, with a finely granular surface A piece was removed for study The spleen was large and was covered by omentum, which prevented its direct visualization Examination of the sections of the liver revealed an extensive multilobular type of cirrhosis, with large amounts of brownish, iron-containing pigment (hemosiderin) in a distribution characteristic of hemochromatosis

The results of laboratory tests, in addition to those presented in tables 1 and 2, were as follows The basal metabolic rate on January 28 was +2 per cent and the urine was the same as on the previous admission With the patient on a low calcium diet (110 mg daily) and a moderate phosphorus intake (700 mg), the three day urinary calcium excretion was 251 mg and the phosphorus excretion 1,214 mg

TABLE 1—*Laboratory Data*

	9/12/3	9/24	10/12	10/25	1/16-17	2/21	2/28
Hemoglobin (per cent)	75		67		65	78	112
Red blood cells (per cu mm)	3,500,000		3,300,000		3,600,000	3,700,000	5,330,000
White blood cells (per cu mm)	5,100		2,650		2,120	3,300	13,800
Blood urea nitrogen	10.16						12.4
Urea clearance (per cent)	75						
Serum calcium	9.36				10.2		
Serum phosphorus	3.3				3.5		
Serum phosphatase (units)	1.1			19.1	23.3		
Serum protein (Gm)	7.6				7.08	6.96	9.2
Serum albumin (Gm)	4.16				3.07	3.28	
Serum globulin (Gm)	3.46				4.01	3.68	
Serum chloride					375		362
Total cholesterol (mg)	490	398		275	325	336	
Ester cholesterol (mg)	333	242		242	114	230	
Free cholesterol (mg)	157	156		33	211	106	
Direct van den Bergh test	+	+	+	+	+	+	
Serum bilirubin	5.6	1.9	5.8	5.1	7.0	3.2	
Bromsulphalein retention (%)	10	0	10	50	80	20	
Hippuric acid excretion (Gm)		1.04				0.72	
Urobilinogen in urine (dilution)	1:100	1:200	1:200	1:400		1:400	

TABLE 2—*Dextrose Tolerance*

Hours after 100 Gm dextrose	Dextrose Mg per 100 Cc of Blood							
	0	½	1	2	3	4	5	6
9/13/38	83	166	176	114				
1/23/39	70	114	157	164				
2/22/39	79		143	114	106	74	70	80

On the third morning of the Cutler test regimen (adrenal cortical function), the chloride concentration in the urine was 362 mg per hundred cubic centimeters

Sex hormone studies (Dr A Rakoff) on February 11 showed gonadotropic hormone (blood and urine), normal or slightly deficient, estrogenic hormone (blood and urine), normal, and androgen (urine), deficient

The patient complained of anorexia and profound weakness, both increasing progressively Beginning on February 3 he was daily given the following medication ascorbic acid, 100 mg, nicotinic acid, 300 mg, thiamine hydrochloride, 1 mg (intramuscularly), and brewers' yeast (powdered), 90 Gm His appetite and strength improved steadily during the next three weeks The xanthomatous lesions became distinctly smaller, many of the smaller areas disappearing The cutaneous pigmentation appeared to be distinctly less marked The scars from the removal of skin for biopsy were not unduly pigmented

On February 27 the patient complained of sudden, severe periumbilical pain The abdomen was distended, but there was no rigidity and peristalsis was audible

The next day at 11 a m, he suddenly collapsed into a shocklike state, with extreme dyspnea, cyanosis and pulmonary edema. The blood pressure was 78 systolic and 56 diastolic, and the venous pressure was 50 mm of water. There was exquisite tenderness over the liver and umbilical region. The patient was placed in an oxygen tent and received dextrose, saline solution and an extract of adrenal cortex intravenously, with no beneficial effect. Death occurred the same day, about twenty-four hours after the sudden onset of abdominal pain. The autopsy was performed by the late Dr B L Crawford.

Gross Observations at Autopsy—The skin of the entire body was dark steel gray, that over the face and neck being darkest. There were numerous small circumscribed yellow areas on the cutaneous surface, more numerous over the face and upper extremities than elsewhere. There was no edema. There was a large scrotal hernia on the left side and a smaller one on the right. There was moderate clubbing of the fingers.

Serous Cavities There was a small amount of yellow, turbid fluid in the peritoneal cavity, with a small amount of fibrinous exudate on the visceral peritoneum. The omentum was adherent to the liver, the abdominal wall and the large hernial sacs on both sides of the scrotum. The pericardial cavity was normal. The left pleural cavity was practically obliterated by dense adhesions, and the right contained about 500 cc of slightly turbid fluid.

Heart The organ weighed 390 Gm and showed no significant change.

Lungs The left lung weighed 1,010 Gm, the right, 850 Gm. Both were markedly anthracotic. On section, considerable blood and frothy fluid exuded from the cut surface. The tracheobronchial lymph nodes were enlarged, softened and anthracotic.

Spleen The organ weighed 1,050 Gm and was 26 by 14 by 6 cm. The capsule was markedly thickened, about two thirds of the anterior surface being hyalinized. The splenic pulp was rather firm and red and contained numerous small, darker red areas.

Adrenal Glands The glands were rather soft but showed no other gross abnormality.

Kidneys The left kidney weighed 150 Gm, the right, 180 Gm. The capsule stripped readily, leaving a smooth surface. On section, there were numerous small yellow flecks in the cortex and medulla, most numerous in the pyramids. The relation between the cortex and the medulla was not altered.

Prostate The gland was slightly enlarged and contained a small nodule in each lateral lobe.

Testes The testes were small and compressed by the hernial sacs. On section, the gland structure appeared to be atrophied.

Gastrointestinal Tract There was pigmentation of the duodenum and the first portion of the jejunum.

Liver The organ weighed 3,170 Gm and was 36 by 23 by 9 cm. It was irregular in outline and was adherent to the surrounding structures. It was firm, and the surface was finely nodular. On section, it appeared dark gray (slate colored), peppered with small yellow areas. The normal lobular markings were not apparent. There was no evidence of obstruction of the biliary passages (extrahepatic), but the gallbladder was greatly distended and filled with thin, light bile.

Pancreas The pancreas weighed 250 Gm. Its consistency varied in different areas. In firmer portions the tissue was dark brown. Near the head there was an extensive area of necrosis and hemorrhage.

Abdominal Lymph Nodes These were enlarged and dark brown

Bone Marrow The bone marrow of the right femur was soft, friable and putty-like

Brain (Dr B J Alpers) The weight was 1,230 Gm The meninges were clear and translucent There was a slight brownish discoloration over the cerebral hemispheres, and the cerebral vessels exhibited slight atherosclerosis On section through the splenium of the corpus callosum a small bluish gray area was noted in the centrum ovale of the right cerebral hemisphere There was also some grayish discoloration dorsal to the right pyramid on section through the pyramidal decussation The hypophysis was grossly normal

Other organs The thymus, thyroid, larynx, bladder and ureters appeared normal

Microscopic Observations at Autopsy—The following were the significant histologic observations

Skin There were an increase in melanin in the normal situation, some fibrosis of the true skin and focal areas of xanthomatous change There was no evidence of hemofuscin or of iron-containing pigment (berlin blue stain)

Thyroid There was a small amount of brownish pigment, which reacted positively with the iron stain

Lung The pleura was thickened and infiltrated with carbon The alveolar walls were somewhat thickened, and anthracotic pigment was deposited throughout the lungs

Heart There was no significant change Careful study revealed no significant deposition of pigment about the nuclei of the muscle fibers

Spleen The capsule was markedly thickened The malpighian corpuscles were somewhat atrophic, and the centers were filled with blood There was proliferation of the fibrous tissue, and the sinusoids stood out prominently, owing to their engorgement with blood There was an extensive deposition of iron-reacting pigment throughout the organ, principally in the cells lining the sinusoids

Liver The capsule was greatly thickened There was a marked increase in the perilobular connective tissue, with some invasion of the lobules The latter were much diminished in size, and there was widespread degeneration of the hepatic cells There was an attempt in some areas at regeneration of bile ducts and liver cells There were small foci of inflammatory reaction throughout the fibrous tissue, which contained an enormous amount of brown, iron-reacting pigment, which was also present in the hepatic cells and, to a larger extent, in the Kupffer cells

Pancreas There was considerable postmortem change However, no areas of fat necrosis were observed There was a slight increase in fat and in interlobular fibrous tissue The most marked feature histologically, apart from the area of necrosis and the hemorrhage noted grossly, was the extensive infiltration of the pancreatic tissue with a brown, iron-reacting pigment

Adrenal Glands There was extensive deposition of iron-reacting, brown pigment in the cortex

Pituitary Gland (Dr B J Alpers) Large amounts of granular, iron-containing pigment were seen in the cells of the anterior lobe

Testes Slight atrophy of the tubules was noted A moderate amount of brown, iron-reacting pigment was present in the interstitial tissue

Retroperitoneal Lymph Nodes The sinuses were dilated There was an enormous amount of iron-reacting, brown pigment, which obscured much of the histologic picture

Brain (Dr B J Alpers) Large amounts of granular, iron-reacting pigment were present in the epithelium of the choroid plexus

Chemical Studies of Tissue—Pieces of tissue were taken for chemical analysis, the iron being determined by the method of Farrar¹ and the final determination being made colorimetrically according to the method of Kennedy² The iron content of the various tissues is presented in table 3

TABLE 3—*Iron Content of Tissues (Grams per Hundred Grams Dry Weight)*

Organ	Weight, Gm	Iron, per Cent Dry Weight	Total Iron, Gm
Liver	3,170	7.23	45.33
Pancreas	250	5.84	3.52
Retroperitoneal lymph node		15.31	
Thyroid		0.71	
Spleen	1,050	0.50	1.26
Heart	390	0.20	
Skin		0.06	
Adrenal		0.32	
Small intestine		0.13	
Kidney	330	0.19	
Testis		0.09	
Skeletal muscle		0.05	
Liver copper, 0.004 Gm per 100 Gm dry weight			

COMMENT

This case presents several unusual features. When the patient was first seen, the diagnosis of hemochromatosis was suggested immediately by the apparently characteristic color of the skin and the presence of an enlarged, hard liver. However, certain other observations cast doubt on this diagnosis, which, in fact, was not established until the second admission to the hospital, about six weeks before death. These confusing facts were (1) the absence of glycosuria and the only slightly abnormal dextrose tolerance curves, (2) the presence of cutaneous xanthomatosis and hypercholesteremia, (3) the absence of iron-containing pigment from the apparently typically pigmented skin and (4) the relatively marked degree of splenomegaly. These discordant features, with the hyperbilirubinemia, led to the tentative diagnosis of xanthomatous biliary cirrhosis (Thannhauser and Magendantz³). This condition is supposedly dependent on, or at least associated with, biliary obstruction due to xanthomatous lesions in the extrahepatic bile passages. Two features present in this case were not in complete accord with this diagnosis: (1) the definitely blue-bronze color of the skin, particularly of the face, and (2) the relatively slight degree of retention of bromsulphalein.

1 Farrar, G. E. The Determination of Iron in Biological Materials, *J. Biol. Chem.* **110** 685, 1935.

2 Kennedy, R. P. The Quantitative Determination of Iron in Tissues, *J. Biol. Chem.* **74** 385, 1927.

3 Thannhauser, S. J., and Magendantz, H. The Different Clinical Groups of Xanthomatous Diseases. A Clinical Physiological Study of Twenty-Two Cases, *Ann. Int. Med.* **11** 1662, 1938.

(10 per cent) on admission as compared with that of bilirubin (5.6 mg). In our experience, this is unusual in obstructive jaundice. However, varying degrees of pigmentation of the skin were reported by Thannhauser and Magendantz³ in xanthomatous biliary cirrhosis, and it is conceivable that the hyperbilirubinemia might be dependent largely on hepatocellular damage rather than on biliary obstruction. Under these circumstances this discrepancy between dye and bilirubin retention is not uncommon. No xanthoma cells or other lipid-containing cells could be found in material obtained by sternal and splenic puncture.

The diagnosis of hemochromatosis was established by histologic examination of a piece of liver removed at peritoneoscopic examination. This necessitated reinterpretation of the observations made previously and led to further studies that might be of interest in this condition. The subsequent course and the observations at necropsy, although confirming the diagnosis, did not explain certain of the puzzling and unusual manifestations presented by this patient. These, with certain additional interesting observations, will be discussed individually.

Absence of Glycosuria—The absence of glycosuria is not in itself a rare phenomenon in cases of hemochromatosis. According to Sheldon,⁴ glycosuria was absent in 22 per cent of 236 cases collected from the literature. In the majority of these, however, no studies were made of the dextrose tolerance, and it is probable that a state of latent diabetes was present in many instances. This was true in at least 3 cases (Evans,⁵ Sheldon⁶ and Yater, McNabb and Horgan⁷). Three dextrose tolerance tests were performed in the present case. The fasting blood sugar concentrations were normal. The first curve (Sept. 13, 1938) suggested slightly diminished tolerance, the second (Jan. 23, 1939), more marked impairment, and the third (February 22), very slight impairment. The first and third curves were of the type not infrequently observed in patients with hepatocellular damage of the extent present here and could be explained on this basis alone.

The extensive acute degeneration of the pancreas incident to the terminal episode unfortunately precludes any accurate estimate of the extent of previous change in the islands of Langerhans. However, according to Sheldon,⁸ diabetes appears to be present invariably in cases in which the concentration of iron in the pancreas is above 1.5 per cent, increasing in severity as the quantity of pigment increases. On this

4 Sheldon, J. H. *Haemochromatosis*, London, Oxford University Press, 1935.

5 Evans, G. *Bronzed Diabetes*, *Proc. Roy. Soc. Med.* **24**: 477, 1931.

6 Sheldon, J. H. *Haemochromatosis*, *Lancet* **2**: 1031, 1934.

7 Yater, W. M., McNabb, P. E., and Horgan, E. *Clinico-Pathologic Types of Haemochromatosis*, *M. Ann. District of Columbia* **1**: 28, 1932.

8 Sheldon (footnotes 4 and 6).

basis, diabetes should certainly be expected with an 110n content in the pancreas of 5.84 per cent. In the absence of information regarding the condition of the islet cells, no satisfactory explanation for the absence of glycosuria and of significantly decreased dextrose tolerance (except temporarily) can be offered. However, in the light of the evidence of adrenal cortical insufficiency, as indicated by the supernormal chloride concentration in the urine in the test proposed by Cutler,⁹ the possible influence of this factor in mitigating or preventing diabetic manifestations should receive consideration. The usually heavy pigmentation of the anterior lobe of the hypophysis suggested to Sheldon⁴ that defective function of this organ may be implicated in the mechanism of increased sensitivity to insulin frequently exhibited by patients with hemochromatosis. In view of present knowledge of the role of the adrenal cortex in carbohydrate metabolism, the observation recorded here may have a similar significance.

Hypogonadism and Hypocorticoadrenalism—Hypogonadism, with loss of sexual desire, impotence and loss of hair, with alteration in its texture (soft, fine and silky), occurs rather frequently in hemochromatosis. According to Sheldon,⁴ it probably ranks next to the classic triad of symptoms in order of frequency. As in this case, the testes are usually small and soft, and atrophy of the germinal epithelium is frequently observed. Labbé and his associates¹⁰ applied the designation "hepatopancreaticogenital syndrome" to this phenomenon occurring in association with hemochromatosis. They attributed the changes in secondary sex characteristics to those in the testes, the cause of the latter being unknown. It is interesting that these organs are usually not heavily pigmented.

As pointed out by Sheldon,⁴ the rather constant occurrence of pigmentation of the anterior lobe of the hypophysis and the adrenal cortex suggests that hypofunction of one or both of these glands may be of fundamental importance in this connection. This hypothesis was supported by his observation in two instances that the basophils of the anterior lobe of the hypophysis were much more deeply pigmented than the eosinophils. In the present case, there was a large amount of hemosiderin in this situation. However, the observation of a distinct deficiency in excretion of androgen, in conjunction with an essentially normal or, at most, only slightly deficient quantity of gonadotropic hor-

9 Cutler, H. H., Power, M. H., and Wilder, R. M. Concentrations of Sodium Chloride and Potassium in the Urine and Blood. Their Diagnostic Significance in Adrenal Insufficiency, *J. A. M. A.* **111** 117 (July 9) 1938.

10 (a) Labbé, M., Boulin, R., Azerad, E., and Uhry. Diabète bronze avec infantilisme tardif, *Bull. et mem. Soc. med. d'hôp. de Paris* **47** 542, 1931. (b) Labbé, M., Boulin, R., and Petresco, M. Etude histologique d'un cas de cirrhose pigmentaire du foie avec diabète et infantilisme régressif, *ibid.* **48** 440, 1932.

none in the blood and urine, suggests that the hypogonadism is perhaps not of hypophysial origin. No definite statement can be made, on the basis of the findings in this case, of the underlying cause of the hypogonadism, but the demonstration of evidence of corticoadrenal hypofunction raises the question as to whether this factor may be related to the testicular changes.

Several authors have attributed certain of the manifestations of hemochromatosis to an associated state of adrenal cortical insufficiency, emphasizing the resemblance to features of Addison's disease. Chief among these are (1) the brownish discoloration of the skin, with an increase in melanin in the malpighian layer, (2) weakness and (3) hypotension. The last is perhaps in part contributed to by the accumulation of pigment in the cardiac muscle fibers. In the present case, the average blood pressure was about 100 systolic and 60 diastolic, with no clinical, electrocardiographic or histologic evidence of significant myocardial damage. The iron content of the heart muscle (0.2 per cent) was distinctly increased (average normal 0.04 per cent) but was not very high as compared with values reported for this condition. The observation of a urinary chloride concentration of 362 mg per hundred cubic centimeters, under conditions of the test procedure described by Cutler,⁹ suggests the presence of a state of impaired function of the adrenal cortex. At the time of the terminal collapse, with marked fall in blood pressure, low venous pressure and evidence of hemoconcentration, the possibility of a crisis of adrenal insufficiency was considered, but active therapy with dextrose, sodium chloride and extract of adrenal cortex was without effect. The normal urea nitrogen content of the blood and the chloride content of the plasma at that time were not in accord with this diagnosis. The demonstration of evidence of cortical functional impairment seems significant in view of the heavy deposition of pigment in this situation.

Hypercholesteremia and Xanthomatosis—These conditions have been rarely observed in association with hemochromatosis, and, as stated by Sheldon,⁴ when hypercholesteremia does occur it is probably attributable to diabetes. Abel, Girard and Kissel¹¹ and Dvorak¹² reported extremely high values, the former 1,180 mg and the latter 1,025 mg per hundred cubic centimeters. It is interesting to note that the patient reported by Dvorak¹² presented some features identical with those in the present instance, viz, icterus, hypercholesteremia, xanthomatosis and pigmentation of the skin, the iron content of which was apparently

11 Abel, E., Girard, J., and Kissel, P. Étude anatomo-clinique d'un cas de diabète bronze, *Rev. med. de l'est* **61** 1, 1933.

12 Dvorak, R. Zur Kenntnis der Hamochromatose, *Munchen med. Wchnschr* **76** 743, 1929.

not increased. This case is not accepted as a genuine one of hemochromatosis by Sheldon,⁴ nor could ours have been in the absence of opportunity to study tissues other than the skin. Becker¹³ reported a case of hemochromatosis associated with so-called Schamberg's disease (progressive pigmentary dermatosis with a high cholesterol content of the blood), in which the cholesterol content of the plasma was 296 mg per hundred cubic centimeters. However, the characteristic features of that condition were not present in the case described here (diffuse, yellow-brown discoloration, erythematous puncta and thinning of the epidermis, with disappearance of the interpapillary processes).

These manifestations (hypercholesteremia and xanthomatosis), occurring in the absence of glycosuria, significantly decreased dextrose tolerance and demonstrable deposits of hemosiderin or hemofuscin in the skin or epithelial cells in the urinary sediment and in the presence of icterus and splenohepatomegaly, led to a presumptive diagnosis of xanthomatous biliary cirrhosis. This was, of course, abandoned later. The cause of this unusual complication and its possible relation to the hemochromatosis remain in doubt. There was no obstruction of the extrahepatic bile passages, and in our experience xanthomatosis and hypercholesteremia with a normal total cholesterol-cholesterol ester ratio are rarely observed in portal cirrhosis or in hepatocellular types of jaundice. It may be pointed out that this ratio, previously normal, fell to 35 per cent (January 16) simultaneously with other evidence of increased impairment of hepatic function (table 1).

Cutaneous Pigmentation—Neither absence of pigmentation nor absence of iron-containing pigment in the skin is rare in hemochromatosis (15 to 20 per cent). This subject has been discussed in detail by Sheldon,⁴ who stated the belief that whereas the bronze color may be due merely to an increase of melanin in the malpighian layer, as in the present case, the metallic blue type of pigmentation is more likely to be associated with the deposition of hemosiderin in superficial layers of the skin. The latter could not be demonstrated in this patient, despite the distinctly blue color. This, however, was most pronounced in the skin of the face, the tissue of which was not examined histologically. The iron content of the skin was, however, increased. It is noteworthy also that, contrary to the usual finding, scars on the skin were only slightly pigmented.

Decrease in the intensity of pigmentation is not uncommon, either spontaneous or following administration of insulin. Consequently, no special significance can be attributed to the progressive diminution in pigmentation observed shortly after the administration of ascorbic acid.

13 Becker, S. W. Schamberg's Disease Associated with Hemochromatosis, *Arch. Dermat. & Syph.* **24**: 380 (Sept.) 1931.

and vitamin B complex was begun. It is interesting, however, that appetite and strength improved simultaneously and that the xanthomatous lesions decreased in size, some disappearing completely. No attempt was made to eliminate cholesterol from the diet, which was high in protein and carbohydrate and low in fat. There have been several references recently to decrease in the intensity of pigmentation in Addison's disease following the administration of ascorbic acid,¹⁴ and the relation of the latter to the metabolism of melanin and its precursors has been demonstrated.¹⁵ The influence of ascorbic acid and the vitamin B complex on xanthomatous lesions merits further investigation.

General Features—The spleen was unusually large (1,050 Gm). In the series of 311 cases collected by Sheldon⁴ the spleen ranged in weight from 114 to 950 Gm, the average being 416 Gm. The iron content of the liver and pancreas was also unusually high, the former containing about 45 Gm (7.23 per cent dry weight) and the latter about 3.5 Gm (5.84 per cent dry weight). The average iron content of the liver in 42 cases reviewed by Sheldon⁴ was 21.36 Gm (highest 38.7 Gm). Incidentally, the copper content was not significantly high (0.004 per cent). As is true in the majority of such cases, the highest concentration of iron was found in the retroperitoneal lymph nodes (15.3 per cent). One unusual finding, in view of the enormous amounts of iron present elsewhere, was the relatively low iron content of the skeletal muscle (psoas) and the heart muscle, about two and five times normal, respectively (table 2).

The cause of death was apparently unrelated to the condition of hemochromatosis, in which death is usually due to diabetic coma (50 per cent), cirrhosis (11 per cent), pneumonia (10 per cent), tuberculosis (9 per cent), carcinoma of the liver (7 per cent), myocardial failure and intercurrent infection. Autopsy revealed extensive necrosis of the pancreas. There was no evidence of fat necrosis, and no cause for the lesion could be demonstrated. Clinically, the acute terminal episode suggested a crisis of adrenal insufficiency or some abdominal catastrophe, and, viewed in retrospect, acute pancreatic necrosis should have been suspected.

14 Cantarow, A. Vitamins, *Internat Clin* **1** 221, 1940. Cornbleet, T. Vitamin C and Pigment, *Arch Dermat & Syph* **35** 471 (March) 1937. Morawitz, P. Pathologische Hautpigmentierung und "Pigmentvitamine," *Klin Wchnschr* **13** 324, 1934.

15 Sealock, R. R., Ziegler, B., and Driver, R. L. The Relation of Vitamin C to the Metabolism of the Melanin Pigment Precursors, Tyrosine and Dihydroxyphenylalanine, *J Biol Chem* **128** 193, 1939. Sealock, R. R., and Silberman, H. E. The Control of Experimental Alcaptonuria by Means of Vitamin C, *Science* **90** 516, 1939. Levine, S. Z., Marples, E., and Gordon, H. H. A Defect in the Metabolism of Aromatic Amino Acids in Premature Infants. The Role of Vitamin C, *ibid* **90** 620, 1939.

SUMMARY

A case is presented of hemochromatosis without glycosuria or iron-containing pigment in the skin, which, however, was blue-bronze in color. The absence of these features, together with the presence of cutaneous xanthomatosis and hypercholesteremia and hyperbilirubinemia, caused considerable difficulty in diagnosis. The true nature of the condition was established by examination of a piece of liver removed at peritoneoscopic examination. Evidence was obtained during life of deficiency in adrenal cortical hormone and in androgen. The possibility was suggested that the diabetic tendency which might otherwise have been present might have been mitigated by the existing state of hypoadrenocorticism. Chemical examination of the tissues revealed enormous quantities of iron in the liver, pancreas and retroperitoneal lymph nodes and relatively little in the heart and skeletal muscle. Death was due to the unusual complication of acute pancreatic necrosis.

ESTIMATION OF RENAL FUNCTION WITH THE AID OF AN IODOSECRETORY INDEX AND A NEW UREOSECRETORY INDEX

AN IMPROVED APPLICATION OF THE CREATININE
METHOD FOR DETERMINING DIURESIS

JOHAN T PETERS, MD

Privatdocent at the University of Leyden, Chief Physician of Clinics for
Internal Diseases in The Hague and Haarlem (Netherlands)

NEW YORK

It is the object of the examinations and observations described in this article to obtain more accurate results in the estimation of renal function

For this purpose it is recommended to use an iodosecretory index, obtained after administering an iodide Should this not be possible or not be allowed, it is advised to replace this iodosecretory index by a new ureosecretory index Both indexes have been deduced from the improved laws of Ambard, and the manner in which this has been done is described

In 1919 I described a formula for the application of Ambard's laws in the diagnosis of renal diseases This formula had certain advantages over the formula deduced by Ambard himself from his laws¹ It appeared, however, that the new formula was endowed with some hereditary taint, for in 1921 Austin, Stillman and Van Slyke,² examiners at the Rockefeller Institute of New York, established the fact that one of Ambard's laws is inaccurate From this discovery it follows that all the formulas deduced from Ambard's laws must be considered worthless This also applies to McLean's index, in which Ambard's coefficient was converted in such a manner that the value taken as a norm was 100 In the following pages I shall try to prove that also the urea clearance test deduced from the improved laws of Ambard and set up by the aforementioned examiners not seldom produces unreliable results and, further, that with the aid of these improved laws more reliable formulas can be set up when urea is replaced by iodine The "iodosecretory index" recommended has produced more reliable results, and the chemical examination according to iodine determination described in this article is simpler and takes up less time than the urea determination

1 Ambard, L, and Weill, A J de physiol et de path gén 14 753, 1912

2 Austin, J H, Stillman, E, and Van Slyke, D D J Biol Chem 46 91,
1921

The conviction is growing that for determination of renal function all one-sided methods of examination, i. e., all methods in which the blood alone or the urine alone is examined, depend too much on extrarenal influences. No such method has escaped this source of mistakes, neither Korányi's cryoscopic test, nor Strauss's rest nitrogen determination,³ nor Widal's⁴ blood urea determination, nor Volhard's concentration and dilution test,⁵ nor Schlayer's potassium iodide or lactose test,⁶ nor Rowntree's phenol red test⁷ nor any of the many other tests with provoked eliminations. I saw that a great deal of time was lost in all these tests, of which it is now ascertained that their reliability does not justify the enthusiasm with which they were welcomed in many clinics. I have no intention to enter here into further details, but I refer the reader to the critical views of Chabanier and Lobo-Onell,⁸ which are in accordance with my experience. These authors strongly recommended the combined methods of examination, i. e., the methods in which parts of blood and urine are taken in mutual correlation. The time has come to control always the one-sided methods by means of combined methods. Nobody will deny the greater advisability of spending more time on a reliable examination than of applying so-called simple methods which, in many cases, even if applied with all possible corrections, cannot stand scientific criticism. A thing worthy of note is that Chabanier and Lobo-Onell were by no means blind to the mistakes entailed by clinging to the combined method, called the constant, or coefficient, of Ambard, recommended by them. They acquainted themselves with the aforementioned improvements of Ambard's laws, and they moreover pointed out the frequent occurrence of a relative oliguria with regard to urea, which makes all ureosecretory constants worthless. Yet, unconceivably, they kept recommending Ambard's coefficient. Probably the reason is that the application of a combined method with the aid of a sulfate or an iodide (with which they were also acquainted) met with practical difficulties. These methods required chemical determinations, which took much time and which must be left to a professional chemist. To surmount these difficulties the firm of Hellige has made, on my request, special sliding glasses by means of which determinations of the level of iodine in blood and urine can be made in a manner sufficiently accurate for clinical purposes.⁹

3 Strauss, H. Die chronischen Nierentzündungen in ihrer Einwirkung auf die Blutfliessigkeit, Berlin, A. Hirschwald, 1902.

4 Widal, F., and Javal, A. *Compt rend Soc de biol* **57** 301, 1904.

5 Volhard, F. *Verhandl d deutsch Kong f inn Med* **27** 735, 1910.

6 Schlayer and Takayashi. *Deutsches Arch f klin Med* **101** 333, 1911.

7 Rowntree, L. G., and Geraghty, J. T. *Tr Am A Genito-Urin Surgeons* **5** 59, 1910.

8 Chabanier, H., and Lobo-Onell, C. *Exploration fonctionelle des reins*, Paris, Masson & Cie, 1930.

9 See note at end of article.

In a number of cases it is difficult (practically speaking, even impossible) to establish whether during the examination there will be a relative oliguria with regard to urea. For this reason it is advisable as a rule to determine the iodosecretory index. In several cases I was led astray by the ureosecretory index. This index may be reserved for cases in which administration of iodine preparations is not advisable or not allowed (e. g. cases of exophthalmic goiter), for cases in which a relative oliguria with regard to urea can be excluded with certainty or for those in which, for want of the necessary means to determine the level of iodine in blood and urine, one has to make the more cumbersome urea determinations. For instance, in a case of disease of the kidneys when there are disturbances of circulation as well, it is very difficult to establish whether a relative oliguria with regard to urea can be excluded. Clinically speaking, oliguria in general is sometimes out of the question, and yet there is a relative oliguria with regard to urea, because the maximum concentration for urea secretion has strongly diminished in consequence of the disease process in the renal parenchyma. Thus a diuresis of more than 1.5 liters can be attended with relative oliguria with regard to urea. This fact is too often overlooked. In 1919, Ambard and Papin¹⁰ pointed out this fact. There no longer exists free play between urea in blood and urea in urine when the latter has reached its maximum concentration. With healthy kidneys this happens at a level of urinary urea of about 50 to 55 Gm per liter, but with pathologic kidneys this value may fall to 10 Gm per liter or less. Inaccurate results of the determinations with Van Slyke's urea clearance test were often obtained in cases of relative oliguria with regard to urea. This relative oliguria also deserves consideration in cases of edema, whether the edema is due to cardiac or to renal disease. Sometimes a relative oliguria with regard to urea may be based on a nervous condition, as I have been able to observe. All this makes one doubt whether in a certain case a relative oliguria with regard to urea does not render useless the trouble taken in making accurate determinations with Van Slyke's urea clearance test. It is an ascertained fact that a deficiency of salt in connection with hyperazotemia is not founded on some fantastic defense reaction, as Blum and his associates¹¹ contended, but is founded on a relative oliguria with regard to urea. The fact that every substance secreted by the kidneys has a certain maximum concentration and that the maximum concentrations of different substances are isomolecular made examiners look for substances the molecular weight of which is great enough to obviate the aforementioned difficulties caused by urea with its relatively low molecular weight. Moreover, it is known that the

10 Ambard, L., and Papin, E. *Arch. internat. de physiol.* 8:437, 1919.

11 Blum, L., Grabar, P., and Van Caulaert, C. *Ann. de med.* 25:34, 1934.

maximal concentrations for the different substances are dependent on the renal parenchyma but are independent of other substances secreted by the kidneys at the same time. To establish a limit value in a certain case (e. g., for urea by administering large quantities of urea or milk) is not only troublesome for the patient but cannot be carried out in many cases on account of nausea or polyuria. Such methods must be left out of consideration.

Before entering into details concerning the iodosecretory index, I shall discuss a few objections raised against these methods of examination. Then I shall explain the improvements which I made in setting up the formulas. These improvements apply to both the iodosecretory and the ureosecretory index.

In 1918, Addis¹² subjected Ambard's laws to a severe criticism. He made extensive examinations in order to compare the secretion of blood urea and of urinary urea under different conditions. In 1921, Austin, Stillman and Van Slyke² ascertained the fact that one of Ambard's laws is inaccurate. In contrast with Addis' observations, they were of the opinion that the proportion between urea secretion and urine volume is altered when the diuresis has reached a certain limit. This limit they called the "augmentation limit." Addis and Drury¹⁴ opposed this opinion, but the results of my own examinations of the same persons, made repeatedly at short intervals, were consistent only if I took into account the existence of an "augmentation limit." In the opinion of the physiologist Peters,¹⁵ the significance of the "augmentation limit," is still not clear. Holten and Rehberg¹⁶ raised a few objections against the use of urea clearances, but their criticism does not apply to the procedure described by me.

I shall not adopt the name "urea clearance" in the following discussion, because the name "ureosecretory index," used by me¹⁷ in a previously published article, speaks for itself, whereas the expression "urea clearance" needs an explanation, as I know from experience.

Without entering into detail regarding the mistakes made in applying the ureosecretory index, I cannot refrain from pointing out the inaccuracy entailed by giving much fluid or much meat very shortly (e. g., within an hour) before the examination. By the tests of Weil it became a well known fact that when this is done the value for serum urea at the

12 Addis, T. *Am J Physiol* **46** 1, 1918.

13 Footnote deleted.

14 Addis, T., and Drury, D. R. *J Biol Chem* **55** 639, 1923.

15 Peters, J. P. *Body Water. The Exchange of Fluids in the Body*, Springfield, Ill., Charles C. Thomas, Publisher, 1935, p. 263. Peters, J. P., and Van Slyke, D. D. *Quantitative Clinical Chemistry*, Baltimore, Williams & Wilkins Company, 1932.

16 Holten, C., and Rehberg, P. B. *Acta med Scandinav* **74** 479, 1931.

17 Peters, J. T. *Arch f klin Med* **129** 3, 1919.

end of the test often shows a difference of 40 per cent from the value observed at the beginning of the test. This fluctuation in the level of blood urea necessarily results in great fluctuation in the concentration of urea in the urine during the test period. It is only accidental if the average concentration of urea in the urine secreted by the kidney during the test period is equal to that in the urine which passed the kidney at the very time of the blood drawing (with which, in point of fact, one should compare the value for serum urea in order to have the most reliable result for the ureosecretory index). During the test period the curve of secretion of urea in urine proceeds in an irregular manner, with transitory rises and falls. Therefore, drawing blood exactly halfway through the test period does not guarantee reliable results. If chance cooperates, the results are reliable, if, however, chance thwarts one, the results are worthless. Hence it

TABLE 1—*Effect of Recent Ingestion of Meat, Fish, Eggs or Milk*

Patient	Examination	Column A		Column B	
		Ur	U I	Ur	U I
Miss B	1st	0.4	82	0.53	87
	2d	0.36	89	0.465	88
Mr K		0.6	64	0.58	63
Mrs N	1st	0.74	60	0.78	58.5
	2d	0.71	55	0.82	58
Miss W		0.545	41	0.7	46
Mr B		0.6	58	0.67	58

* In column A are mentioned the values for blood urea in grams per liter (Ur) and the ureosecretory index (U I), when for twelve hours no meat, fish, eggs or milk had been taken. In column B the same values are mentioned, when two hours before the examination 200 Gm of beefsteak had been taken. The interval between the first and the second examinations varied from a few days to a few weeks.

is necessary to make such preparations before starting the examination as will prevent great fluctuations of the concentration of urea in the urine during the test period. However, it is unnecessary, as it was formerly advised, to make the examination in the morning before breakfast, unless one wishes to know at the same time the value of serum urea while it is less influenced by previously ingested food. According to my experience, if one sees to it that during five hours before the test moderate quantities of fluid are taken and that neither food nor fluid is taken during the hour preceding the test, reliable results will be obtained. From tests (table 1, column B) which I began to make one hour after 200 Gm of meat had been taken it is seen that the ureosecretory index, even after such an overloading with albumin, deviates strikingly little from values observed when, twelve hours previously, a diet poor in nitrogen had been observed (table 1, column A). All this holds true on condition that no relative oliguria with regard to urea exists. In all cases only the value for serum urea has risen above normal limits. This proves once more that determination of this value only is insufficient to test

renal function It needs no further demonstration that, for the same reason, in determining the iodosecretory index stronger fluctuations of the concentration of iodine in blood and urine should be prevented after administration of an iodide

Some have made the remark that they could not understand how the quantity of renal tissue, an anatomic value, can affect the function of the kidney Of course, cases in which one part of the kidney has received a local injury and in which by consequence another part shows compensatory hyperfunction must be excluded This I shall discuss later However, in normal renal parenchyma, when comparison is made between the diuresis of adults and children, other things being equal, the normal diuresis of healthy kidneys is seen to be reduced in proportion to the decrease in weight of the renal parenchyma This is acknowledged by most writers, such as Ambard, Addis and Conway As determination of the weight of the renal parenchyma proved to be too difficult, they inserted into the formula the factor of body weight, supposing that the body weight ran parallel to the weight of the renal parenchyma Now in this lies a mistake, made by Ambard and Conway It is a still greater mistake to take no account of the renal weight, as in the simplified formula of Van Slyke's urea clearance In his unsimplified formula Van Slyke introduced the factor "surface area," which was supposed to be proportional to the amount of kidney tissue However, one can be sure that in many hospitals the simplified urea clearance is used, since I find in the latest editions of widely read and excellent books (Todd and Sanford,¹⁸ Koch,¹⁹ Levinson and McFate²⁰) only the simplified formula (Osgood²¹ described the urea clearance with the factor "surface area") With neglect of the amount of kidney tissue, a deviation of renal function can be wrongly diagnosed in the case of a small person or a child, because the subject has less renal parenchyma than an adult of normal size and consequently shows a slighter diuresis With renal weights above the average, a deviation can be camouflaged When the weight of the renal parenchyma is replaced by the body weight, the mistake is most evident with sufferers from adiposity or macies and also in a high degree with children That it is not permissible to assume that body weight runs parallel to renal weight I can easily show with the aid of a curve, in which renal weight

18 Todd, J C, and Sanford, A H Clinical Diagnosis, ed 8, Philadelphia, W B Saunders Company, 1935

19 Koch, F C Practical Methods in Biochemistry, ed 2, Baltimore, William Wood & Company, 1937

20 Levinson, S A, and McFate, R P Clinical Laboratory Diagnosis, Philadelphia, Lea & Febiger, 1937

21 Osgood, E E Laboratory Diagnosis, ed 3, Philadelphia, The Blakiston Company, 1940

is indicated in percentage of body weight (figures in left column) at different ages (chart 1) If renal weight and body weight should increase to the same degree in the period of growth, the same proportionate number, expressed in percentage between renal weight and body weight, should be found at all ages, and the curve in chart 1 should show a horizontal line The enormous deviation from the horizontal points out the error made by inserting body weight instead of renal weight into the formulas

In the case of children I refer the reader to anatomic atlases for the striking relative largeness of the kidneys From this it can be concluded at first sight that the ratio of renal weight to body weight and also to surface area is altered during the period of growth Consequently the calculation of Van Slyke's urea clearance also with the

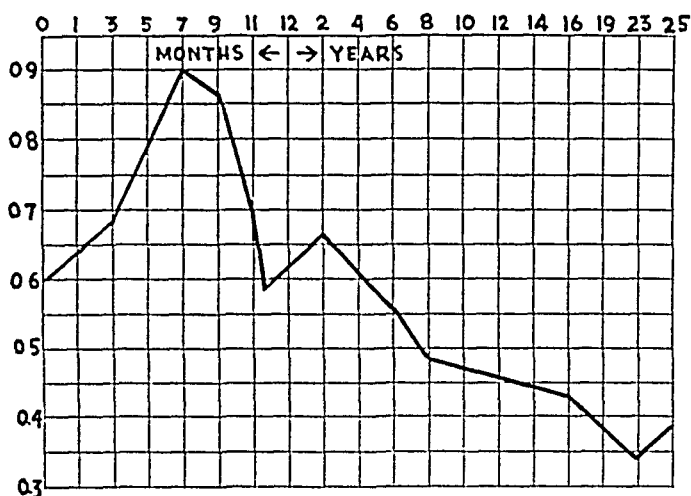


Chart 1—Renal weight in relation to body weight The horizontal column of numbers indicate the age of the subject, the vertical column of numbers indicates what percentage of body weight corresponds at a certain age with the weight of the kidneys

factor "surface area" can produce unreliable results in the cases of children Since anatomic observations, especially in children, refute the conception that the amount of kidney tissue is proportional to the surface area, I tried to solve the problem in another way

The question is how the weight of the renal parenchyma can be calculated in the simplest manner For this purpose I have noted the renal weight and the body height and weight at 100 postmortem examinations of adults and children Instead of the renal weight, I have calculated the weight of the renal parenchyma by subtracting the average weight of the blood, the blood vessels and the basin of the kidneys By this method the renal weight is reduced by one fifth on an average It appears that with persons over 18 years of age the weight in grams of the renal parenchyma may be equated as 1.4 times the body height in

centimeters I found it the simplest method to use the body height as a standard, for with sufferers from adiposity or macies this is still the most reliable standard. With persons under 18 years of age it is advisable to read the weight of the renal parenchyma from a chart made up by me for that purpose (chart 2) because after the age of 12 the quantity of renal parenchyma increases more in girls than in boys. In girls after the age of 14 it again lags behind as compared to that of boys. With this method a simple multiplication is sufficient for adults and the use of a simple curve for children. With this method one escapes also the

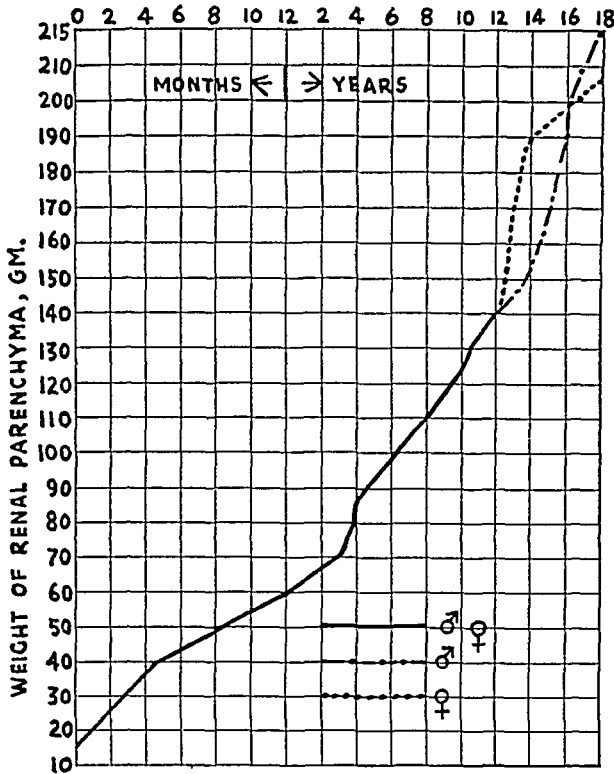


Chart 2—Curve from which can be read the weight of the renal parenchyma in persons under 18 years of age

always more cumbersome use of large tables of "surface areas," and the results are more reliable, especially with children.

I shall now briefly discuss the deduction of the formulas. In 1918 Addis¹² and in 1921 Austin, Stillman and Van Slyke² checked Ambard's two laws. This had already been done, though in a less complete manner, by Marshall and Davis in 1914. Often there has been confusion as to the meaning of the letters used in these formulas. In discussing the deduction of formulas, one must retain Ambard's abbreviations, the meaning of which is as follows. By C is meant the number of grams of urea per liter of urine, and by U , the number of grams of urea per liter of blood. By V is meant the number of

cubic centimeters of urine, and by D (debit), the number of grams of urea, which would have been secreted in twenty-four hours if during those twenty-four hours the diuresis had been of the same grade as the diuresis during the test period. This conversion at twenty-four hours is quite arbitrary. One might as well have chosen sixty minutes or another space of time. I thought it much simpler to calculate the minute volume (M), as American writers also have done. These writers use other letters and express the values for urea nitrogen in milligrams per hundred cubic centimeters (U , urine urea nitrogen in milligrams per hundred cubic centimeters, B , blood urea nitrogen in milligrams per hundred cubic centimeters, V , the number of cubic centimeters of urine per minute, and C , the urea clearance). It cannot be denied that the meanings of these letters created confusion, since the original abbreviations recommended by Ambard are still used in another part of the medical literature.

For the convenience of those who are accustomed to only one form of expression, I shall draw up the formulas for calculation of the indexes in both forms, expressing them, that is, in milligrams of urea nitrogen as well as in grams of urea. The figures for grams of urea should be multiplied by 46.5 to obtain the values in milligrams of urea nitrogen, so that one can simply replace $\frac{C}{U_r}$ by $\frac{U}{B}$. To designate minute volume, however, I advise that the letter M be used instead of the letter V , to avoid confusion with the aforementioned other significance of V in a part of the medical literature. The factor "surface area," used for correction of the urinary minute volume, is canceled and replaced by the factor N (weight [in grams] of the renal parenchyma). The abbreviations which I used in establishing the formulas for the iodosecretory index I shall mention later.

The aforementioned American writers came to the following conclusions:

The first law of Ambard, $K = \frac{D}{ur^2}$, is correct if C remains constant. This condition was also made by Ambard. If C does not remain constant, distinction must be made between cases in which polyuria is present and those in which it is not. These improved laws were ascertained by experiments on dogs. Addis confirmed the results by experiments on rabbits. Ambard's first law must be taken as a particular instance (with C remaining constant) of more general laws.

The second law set up by Ambard proved to be wrong. It ran $k = D \sqrt{C}$, if U_r was constant. This law was valid only if $Ur \sqrt{D}$ was constant.

It is almost generally admitted that the criticism of Ambard's laws was to the purpose and that the new laws set up by the American investigators are correct. However, I looked for contradiction and found it, among other places, in the work of the French writers Chabamier and

Lobo-Onell⁸ They criticized all writers who dared contest Ambard's coefficient It is interesting to know what judgment they passed on the aforementioned American investigations They passed off the matter by saying that Van Slyke²² revoked the results of the aforementioned correction of Ambard's laws However, everybody reading Van Slyke's article sees at once that a revocation is out of the question On the contrary, Van Slyke justly appreciated Ambard's work, but he stated the opinion that the results of his own examination were an improvement

Since the deduction of the formulas by the American writers, I have tried to deduce two new formulas The one new formula applies to cases in which polyuria is present, the other, to cases in which there is no polyuria I have replaced the factor "surface area" by the weight of the renal parenchyma calculated in the aforementioned manner and based on observations at autopsy It may be admitted that if, other things being equal, the diuresis is proportionately altered with the weight of the renal parenchyma the result will remain constant if the minute volume (M) is divided by the weight of the renal parenchyma (N) When the formula suitable for cases in which no polyuria is present is multiplied by 40 (for the iodosecretory index) or by 28 (for the ureosecretory index) and when the formula suitable for cases of polyuria is multiplied by 29 (for the iodosecretory index) or by 20 (for the ureosecretory index), the average result for persons with healthy kidneys is 100 If in a case in which the kidneys are altered by disease a result of (e g) 30 is found, one may conclude that about 30 per cent of the renal tissue is still working sufficiently In contrast with some other formulas, one has at once, without additional calculations, the indication in every case as to what percentage of the renal tissue is still working sufficiently From a great number of examinations in cases of healthy and diseased kidneys I was able to establish that the physiologic fluctuations lie between 60 and 140 Values under 60 point out a pathologic renal hypofunction, and the values above 140 point out a hyperfunction of the renal tissue With the aid of a pocket slide rule, to be mentioned later, the results of these formulas can be read within one minute

After making many experiments, it appeared to me advisable to use the "polyuria formula" when the minute volume (M) is larger than 2 cc, although the limit seems to be somewhat different for different persons With minute volumes of less than 2 cc, which form the majority, I use this formula for cases in which polyuria is not present The same limit is adopted by American investigators I have drawn up the formulas in such a manner that when the minute volume is exactly equal to 2 cc it is immaterial which formula is used

Of course, there are cases in which these formulas cannot be applied I have already pointed out the fact that in the presence of a relative

22 Van Slyke, D D Presse med 35 214, 1927

oliguria with regard to urea the ureosecretory index is worthless, because the urea is secreted at its limit concentration (concentratio maxima). The existence of this relative oliguria cannot be excluded with certainty in many cases. In these cases reliable results are obtained by replacing the ureosecretory index by the iodosecretory index.

That there is a relation between the secretory functions of the kidney with regard to different substances appears from the fact that the limit concentrations of different substances are isomolecular. When a person has a maximal concentration of urea in the urine, e g., 50 Gm in 1,000 cubic centimeters, the limit concentration of this urine with regard to dextrose will be 150 Gm. The molecular weight of dextrose, which is 180, is three times the molecular weight of urea, which is 60. Substances with renal thresholds, like dextrose, are not suitable for examination of the renal function. The substance most suitable, as far as I know, for the purpose is iodine, because it has no renal threshold and its atomic weight is high (127). Supposing that with diseased kidneys the limit concentration for urea in the urine is 10 Gm per liter, the limit concentration for iodine will be equal to 21.1 Gm per liter, because $60 : 127 = 10 : 21.1$. Should a maximum dose of iodine be given, the concentration of iodine will remain far below 21 Gm per liter. Chabamier admitted that it would be possible to obtain a constant value with either healthy or diseased kidneys if in Ambard's formula urea were replaced by iodine. Indeed, his example proved that this replacement was allowable. I applied it, with the same results. In order to obtain for this iodosecretory index the average result 100, the formula must be multiplied by another number than that used for the ureosecretory index. As a result of all these considerations, the following formulas were set up:

$I I$ = iodosecretory index Iu = mg of iodine per hundred cubic centimeters of urine

Ib = mg of iodine per hundred cubic centimeters of blood

$U I$ = ureosecretory index C = Gm of urea per liter of urine U = urea nitrogen in milligrams per hundred cubic centimeters of urine Ur = Gm of urea per liter of blood B = urea nitrogen in milligrams per hundred cubic centimeters of blood

N = weight (in grams) of the renal parenchyma

M = minute volume in cubic centimeters (Designated as V in a part of the literature)

$$\text{When } M < 2, I I = 40 \times \frac{Iu}{Ib} \times \sqrt{\frac{M}{N}}$$

$$\text{When } M > 2, I I = 29 \times \frac{Iu}{Ib} \times \frac{M}{\sqrt{N}}$$

$$\text{When } M < 2, U I = 28 \times \frac{C}{Ur} \times \sqrt{\frac{M}{N}} = 28 \times \frac{U}{B} \times \sqrt{\frac{M}{N}}$$

$$\text{When } M > 2, U I = 20 \times \frac{C}{Ur} \times \frac{M}{\sqrt{N}} = 20 \times \frac{U}{B} \times \frac{M}{\sqrt{N}}$$

How the preparation should be made—and this is of the greatest importance for obtaining reliable results—and how the calculation can be done very quickly will be described in the following pages

With healthy persons and also with patients not showing a relative oliguria with regard to urea, I was able to establish that the results agreed well when both the ureosecretory and the iodosecretory indexes are calculated for the same person. If there is a relative oliguria with regard to urea, only the iodosecretory index can give reliable information. Since the chemical test for the iodosecretory index takes less time, nobody will object to the thesis that as a routine method the determina-

TABLE 2—*Determination of Both Indexes in the Same Examination**

Patient	Examination	M	Iu, Mg per 100 Cc	Ib, Mg per 100 Cc	I I	C	Ur	U I
Miss v N	1st	0.8	380	8	110	24.4	0.36	103
	2d	1	402	9.3	110	26.6	0.45	107
Mrs. B		0.5	300	8	68	23.9	0.436	70
Mr. V. A.		0.65	410	12	71	23.2	0.49	70
Miss A.		2.35	67.5	10.3	29	8.2	0.8	29
Mr. R.		2.1	43	10.5	17.4	7.6	1.07	19

* On the day after the first examination the patient (v. N.) was examined again (verifying examination)

TABLE 3—*Influence of Oliguria on the Ureosecretory Index**

Patient	M	Iu, Mg per 100 Cc	Ib, Mg per 100 Cc	I I	C	Ur	U I
Mr. V. S.	0.318	600	13.2	68	21	0.590	37
Miss W.	0.417	664	11.3	104	20.8	0.465	53

* Instances of low urinary secretion, in which the iodosecretory index only was reliable. In a clinical sense neither Mr. V. S. nor Miss W. suffered from a renal disease.

tion of the iodosecretory index is preferable to that of the ureosecretory index.

I shall first mention some instances which show that the iodosecretory index agrees well with the ureosecretory index when applied to the same person (table 2). In cases in which the agreement was less satisfactory clinical observations advocated the accuracy of the iodosecretory index.

In table 3 are noted the iodosecretory and the ureosecretory indexes of 2 patients, whose slight diuresis during the test period and whose high level of blood urea supported the possibility of a relative oliguria with regard to urea. The results for the iodosecretory index agree with the clinical picture, whereas the results for the ureosecretory index are at variance with it. That the bases on which the formulas rest are solid is clearly demonstrated by the often striking agreement of the

values for the iodosecretory and those for the ureosecretory indexes if a relative oliguria is excluded, notwithstanding quite different values for M , I_u , I_b , C and U_r . Table 4 refers to persons with healthy kidneys. In two successive examinations, the values for I_u , I_b , C , U_r and M sometimes differed greatly whereas the indexes agreed well. In these cases no polyuria was present. Table 5 shows that the existence of an "augmentation limit" must be admitted. For this I selected indexes established in the cases of persons with healthy kidneys who during the

TABLE 4—*Results of Repeated Examinations at Short Intervals**

Patient	Examination	M			
Mr H	1st	1.26	$I_u = 260 \text{ mg /100 cc}$	$I_b = 11.8 \text{ mg /100 cc}$	$I/I = 64$
	2d	1.13	$I_u = 226 \text{ mg /100 cc}$	$I_b = 10.3 \text{ mg /100 cc}$	$I/I = 61$
Miss H	1st	0.97	$C = 15.6$	$U_r = 0.29$	$U/I = 96$
	2d	0.88	$C = 24.5$	$U_r = 0.275$	$U/I = 99$
Miss B	1st	0.54	$C = 22.6$	$U_r = 0.35$	$U/I = 88$
	2d	0.44	$C = 17.3$	$U_r = 0.243$	$U/I = 87$
Mrs B	1st	1.55	$C = 9.7$	$U_r = 0.324$	$U/I = 70$
	2d	0.46	$C = 10.8$	$U_r = 0.189$	$U/I = 73$
Mrs C	1st	0.89	$C = 15$	$U_r = 0.286$	$U/I = 94$
	2d	0.43	$C = 20.28$	$U_r = 0.26$	$U/I = 98$

* This table shows the good agreement in the results when at an interval of a few days the examination of the same person was repeated. The subjects were persons with healthy kidneys, and polyuria was not present.

TABLE 5—*Importance of Selection of Correct Formula in the Individual Case**

Patient	Examination	C	U_r	M	N	UI Formula Intended for Patients with Polyuria	UI Formula Intended for Patients Without Polyuria
Miss D	1st	4.5	0.35	4.5	225	77	51
	2d	2.8	0.285	5.9	225	77	34
Mr L	1st	5.8	0.365	4.15	260	82	56
	2d	6	0.24	2.6	260	81	70
Mrs H	1st	4.85	0.38	4.45	240	73	49
	2d	1.82	0.104	3.1	240	69	56

* This table shows that the clinician obtains a good agreement in the results of the first and in those of the second (verifying) examination only if he uses in the cases of polyuria the formula intended for them and not the formula intended for cases in which no polyuria is present. The patients were persons with healthy kidneys, and in all cases there was polyuria, i. e., M was larger than 2 cc.

test accidentally showed polyuria again and again. To compare them, I made calculations both with the formula set up for cases in which polyuria is present and with the formula set up for cases in which there is no polyuria. One sees at once how good the results are when the "polyuria formula" is used in cases of polyuria and how poor they are with use of the formula for cases in which there is no polyuria.

Table 6 conveys the same meaning. Applying a second test in these cases, I accidentally observed polyuria, which had not been present in the first examination. If the formula was applied in that second test as

in the first examination, the result was much poorer than when the "polyuria formula" was used

Table 7 shows the results of successive examinations of patients suffering from serious Bright's disease Miss W's condition was station-

TABLE 6—Comparative Results with Different Formulas *

Patient	Exami nation	C	Ur	M	N	Results with Suitable U I Formula	Results with U I Formula for Patients Without Polyuria
Mr E	1st	17 6	0 416	1 11	244	80	
	2d	7 8	0 338	2 46	244	73	65
Mr B	1st	30 2	0 7	0 58	238	59	
	2d	5 98	0 416	3 1	238	57 5	46
Mrs A	1st	9 36	0 364	0 95	215	48	
	2d	4 45	0 341	2 5	215	44	40

* This table illustrates cases in which accidentally no polyuria was present in the first examination and in which in the second (verifying) examination polyuria was found Like table 5, it points out the necessity of using the suitable formula

TABLE 7—Results of Successive Examinations *

Patient	Examination	C	Ur	M	N	U I
Miss W	1st	14	1 74	0 67	224	12 4
	2d	17	1 58	0 445	224	13 5
	3d	9 5	1 02	0 45	224	11 7
Mr H	1st	11 4	1 75	1 8	239	16 2
	2d	13	1 89	0 79	239	11 2
Mr V	January 15	8 6	1 22	1 29	230	14 7
	May 22	7 75	1 16	1 17	230	13 4
	May 23	7 55	1 13	1	230	12 4
	December 17	7 5	1 32	1 17	230	11 4
	December 18	8 65	1 3	0 88	230	11 6

* This table shows the successive examinations of patients with renal disease The first case shows that the poor condition of the kidneys remained constant The 2 other cases show the progressive character of the course of the disease, which was also established clinically

TABLE 8—Progressive Decline of Index Values in a Case of Bright's Disease *

Patient	Date of Examination	C	Ur	M	N	U I
Mr L	8/8 36	19 4	0 54	1 02	233	67
	10/8 36	16 7	0 485	0 88	233	58
	7/3 37	10 4	0 442	1 08	233	45
	10/7 37	12 48	0 936	1 3	233	27 5
	11/7 37	9 88	0 884	1 33	233	23 5

* This table shows the steady decline of the ureosecretory indexes in 1 year in the case of a patient with serious Bright's disease

ary, but Mr H's and Mr V's condition had grown worse on the dates of the successive clinical examinations, as is shown by the indexes

Table 8 shows the results of examinations in the course of a year in a case of clinical progressive Bright's disease In that year I determined the ureosecretory index five times One sees the constant decline of the indexes

A difficulty in applying these formulas is that some persons do not empty the bladder completely at the prescribed time. If one suspects retention of urine, a catheterization of the bladder can be applied. Male patients, however, dislike it sometimes to such an extent that they do not allow a second (verifying) examination, which, if possible, I make within a week after the first examination. Moreover, one sometimes is not sure whether the bladder has been completely emptied via the catheter. Many years ago, knowing the examinations in Utrecht of Verploegh and Hoogenhuyze, of which mention will be made later, I tried to make use of creatinine secretion to avoid this source of errors. Later I saw that other investigators also used this means. The fact that Behre and Benedict²³ suggested, that the actual creatinine is not responsible for the change in color, does not detract from the practical value of the creatinine test in this case. As far as I was able to ascertain, physicians had not yet arrived at a systematic application of the creatinine method, because this method takes too much time. It was recommended to make determinations of the level of creatinine in the urine with the aid of solutions of coloring matters which were of a different chemical composition from creatinine and for this reason of a somewhat different color. This difference in color was sufficient to make the determinations unreliable, as was proved by my experience. However, I have now succeeded in simplifying this complicated method so that quantitative determinations of the concentration of creatinine can be dispensed with. This method takes little time and yet produces reliable results, as the verifying test has shown. Only the use of a good colorimeter is required, e g, the Duboscq type of colorimeter or a Zeiss-Ikon colorimeter. I make use of certain well known facts: first, the fact that the patient is nearly always able to empty the bladder more completely when the period of filling is somewhat prolonged than when it is relatively short, and second, that with the same retained quantity the error made in calculating the minute volume will be slighter, as the voided quantity will be larger. Suppose that the kidneys of a person secrete 300 cc of urine in three hundred minutes. The quantity of urine voided is only 270 cc. The amount retained is 30 cc, and the minute volume seems to be $\frac{270}{300} = 0.9$ cc, whereas it is actually $\frac{300}{300} = 1$ cc. The error per minute volume is 0.1 cc. Further, suppose that some hours later the kidneys of the same person secrete 60 cc of urine in the course of sixty minutes. The quantity of urine voided is only 30 cc. The amount retained is 30 cc, as in the former, longer period. The minute volume seems to be $\frac{30}{60} = 0.5$ cc, whereas it actually is $\frac{60}{60} = 1$ cc. The error per minute volume is 0.5 and so five times greater than with the same retained quantity in a five times longer

23 Behre, J. A., and Benedict, S. R. *J Biol Chem* **52** 11, 1922

period of filling of the bladder. Of course, this longer period should not be extended too long, because complaints of dysuria will then arise. A period of about five to five and one-half hours has proved suitable in many cases for application of the creatinine method. The minute volume for this longer period (five and one-half hours), which may be called the preparation period, must be calculated by measuring the quantity of urine for this period. The minute volume for a shorter period (e. g., one hour), which may be called the test period, can be calculated by the application of the creatinine method without measuring the quantity of urine for this period. Incomplete emptying of the bladder after the short test period cannot render worthless the whole examination if emptying of the bladder after the preparation period has been complete.

The creatinine method is based on the fact that practically creatinine is secreted in equal quantities per unit of time in the same person and on the same day. This was demonstrated in 1905 by Veiploegh and Hoogenhuyze at the laboratory of Pekelharing, Utrecht, and confirmed by Schaffer in 1908. Therefore, when two specimens of urine secreted by a patient in one day are compared, the minute volumes of these specimens will be inversely proportional to the concentrations of creatinine. I made use of the fact that these creatinine concentrations themselves are inversely proportional to the volumes which, with similarity of color, are read off on the colorimeter. In this way determination of the creatinine concentrations can be dispensed with, for the conclusion may be drawn that the minute volumes are directly proportional to the volumes read off on the colorimeter (with similarity of color). Standard solutions of coloring matters, which had to be prepared again and again and which, as has been mentioned, never were of exactly the same color as the creatinine, are then also dispensed with. In another way also I succeeded in dispensing with these standard solutions. I saw that the sliding glasses put on the market by the firm of Hellige for determining the concentrations of creatinine in blood are worthless for determining the concentrations of creatinine in urine. Therefore I made an experiment with the Zeiss-Ikon blood sugar meter. The colored glass of this apparatus shows the color of picramic acid (monoaminodinitrophenol) and this color agrees strikingly with the color of the urinary creatinine reaction. The agreement of the results with those obtained with the Duboscq type of colorimeter struck me. In this case the numbers of the Zeiss-Ikon colorimeter are used only as comparison values for the intensity of color. These numbers are directly proportional to the concentrations of creatinine. As has been stated, the latter values are inversely proportional to the minute volumes, whereas these minute volumes are directly proportional to the volumes read off on the Duboscq type of colorimeter. If M^1 is considered the minute volume for the preparation period, K^1 the concentration of creatinine in the urine for

this period, v^1 the volume read off on a Duboscq type colorimeter, and if one calls the same values for urine collected during the test period respectively M , K and v , the result is, as has been mentioned

$$\frac{M}{M^1} = \frac{K^1}{K} = \frac{v}{v^1}.$$

In a certain case, in which M^1 was 0.33, a laboratory assistant, using a Duboscq type of colorimeter, read off $v = 19.1$ and $v^1 = 20$, and I, without knowing these numbers, read off on a Zeiss-Ikon colorimeter $K = 320$ and $K^1 = 310$. In both readings the value for M was exactly the same, 0.318. It does not matter, therefore, which of the two methods is used.

I shall now mention a few instances to show how accurate is the result of the creatinine method.

Miss S, after the test period was past, voided 50 cc of urine. With the aid of the creatinine method I estimated this value at 49.6 cc. Miss W, after the test period was past, voided 25 cc of urine. With the

TABLE 9—Results With and Without Use of the Creatinine Method *

Patient	Examination	O	Ur	N	M Without Creatinine Method	M with Creatinine Method	U I Without Creatinine Method	U I with Creatinine Method
Mr S	1st	8.2	1.5	236	3.26	1.41	24.8	11.9
	2d	8.2	1.45	236	1.12	1.45	11	12.4
Mrs B	1st	21	0.35	214	0.2	0.49	61	92
	2d	21	0.24	214	0.28	0.27	89	88

* This table shows that in these cases the results in repeated examinations agreed much better when the minute volume was determined with the aid of the creatinine method. For further explanation, see text.

aid of the creatinine method, I estimated this value at 25.02 cc. In the case of Mr N, the values were 41.7 and 42 respectively.

It is astonishing what accurate results can be obtained with this simple colorimeter method.

In cases in which I suspected retention of urine at the beginning or at the end of the test period I often found on determination of the iodosecretory or of the ureosecretory index that the results showed more accurate agreement at the first and at the second (verifying) examination if the numbers obtained with the aid of the creatinine method were used than by direct measuring of the quantity of urine.

In table 9 it is seen that at the first examination of Mr S with the creatinine method I found a much lower value for M than by direct measuring without the creatinine method. At the second (verifying) examination of the same subject it was just the reverse, though in a less pronounced degree. The table shows that in calculation of the ureosecretory index the numbers agree well (11.9 and 12.4) if the results of the creatinine method are used. The difference of the results

obtained without applying the creatinine method (24.8 and 11) indicates unreliability. In this case the creatinine method appeared to be indispensable, because catheterization was not allowed by the patient. That the quantity of urine measured at the first examination was much larger than the quantity calculated by the creatinine method is due to the fact that at the beginning of this test the patient showed a retention of urine, whether only at the beginning or in a more marked degree at the beginning than at the end of the test period. At the verifying test the reverse was true.

The second patient, Mrs. B., showed at the first examination a greater retention at the beginning of the test period. That in this case too the results of the ureosecretory index calculated with the aid of the creatinine method were more reliable than the results obtained without applying the creatinine method is shown in table 9 (92 and 88 over against 61 and 89).

Considering these results, one might raise the question whether it is not advisable to apply this simple creatinine method in all cases for determining the diuresis during the test period, especially as the use of the catheter does not guarantee complete emptying of the bladder.

On applying ureteral catheterization for examining the renal function of each of the kidneys separately, one encounters the difficulty that a part of the urine often runs outside along the ureteral catheter into the bladder. With the creatinine method one can establish in a reliable way how much urine is secreted in a certain period by each of the kidneys separately. There exists an ingenious, though simple, calculation to establish (without this creatinine method) how much urine has been secreted by each of the kidneys in a certain period. The two methods can be combined for verifying purposes. When the ureteral catheters have been placed, the water brought into the bladder is allowed to run away through a bladder catheter. Everything depends on whether catheterization of the bladder is done completely, because if it is not done completely the method of calculation is worthless. Suppose that all the water has been removed from the bladder and that from this point of time, during a certain period, x cc of urine runs outside along the right ureteral catheter into the bladder and y cc of urine outside along the left ureteral catheter. When the test is finished, the bladder is again emptied with the catheter. Suppose, further, that the bladder catheter produces vb cc, then $vb = x + y$. When inside, the right ureteral catheter runs a volume of vr cc, and when inside, the left ureteral catheter runs a volume of vl cc. When, further, the number of grams of urea per cubic centimeter in the urine of the bladder is ub and this value for the urine secreted by the right kidney is u and for that secreted by the left kidney is ul , then $(x \times u) + (y \times ul) = vb \times ub$. There are now two comparisons, with two unknowns, with which x and y can be cal-

culated. In reality the right kidney has secreted $(vl + x)$ cc and the left kidney $(vl + y)$ cc. I have described this method here also to demonstrate that examination with the aid of the creatinine method is to be preferred since one can never make quite sure whether the water and, later, the urine have been completely removed from the bladder.

If it is only a matter of comparing the function of the two kidneys, the chromocystoscopic and the pyelographic procedures introduced by Von Lichtenberg and Strick are sufficient. However, it is also of much importance to get an accurate view of the absolute function of a kidney, e. g., a kidney that will be left in the body after unilateral nephrectomy. In such cases the determination of the secretory index gives a reliable insight. It must therefore be combined with chromocystoscopic or pyelographic procedures. Each surgeon in his treatment of urologic patients is often faced with the question whether one kidney (the best of the two or a solitary kidney) functions sufficiently. Application of the aforementioned method can give the correct answer.

TABLE 10—*Examination of Renal Function of a Dog**

	C	Ur	M	N	U I
Before extirpation of one kidney	13	0.3	0.21	40	88
Day after operation	5.1	0.605	1.27	40	51
Three days afterward	7.35	0.456	0.64	40	57

* This table shows the influence on the U I of extirpation of one kidney. The calculations have been made as if it were unknown that one kidney had been removed. (The extirpated kidney weighed 20 Gm., and so it was assumed that both kidneys weighed 40 Gm.)

In applying the secretory indexes, one should always take into consideration that the results of them never give one a right to judge of the anatomic extensiveness of lesions, because other parts of a partly diseased kidney may show compensatory hyperfunction. This general rule must not be overlooked. Compensatory hyperfunction of a healthy kidney often occurs when the other kidney is diseased or has been removed. Examining solitary kidneys, I repeatedly found an index agree with the functional ability of two healthy kidneys. When both kidneys function normally, the secretory index of one of the kidneys, on account of physiologic fluctuations, lies between 30 and 70, averaging 50. Of course the weight of the parenchyma of each of the kidneys must be taken into account. Thus, in one case I found for the function of one kidney (both kidneys appearing to be healthy) a ureosecretory index of 55 if I took into account the total parenchyma of both kidneys and a ureosecretory index of 94 if I took into account half the weight of the total renal parenchyma.

As a verifying test, I asked a surgeon to remove a kidney of a healthy dog. Before and after the nephrectomy I obtained the results given in table 10.

It is now possible to establish before nephrectomy the absolute function of the remaining kidney, independent of a relative oliguria with regard to urea, with the aid of the iodosecretory index and the creatinine method

Reliable knowledge of the renal function may also be of great importance in the differential diagnosis of albuminuria and Bright's disease

A SIMPLE METHOD OF DETERMINING THE CONTENT OF IODINE IN URINE AND BLOOD AFTER ADMINISTRATION OF AN IODINE SALT

The aforementioned advantages of replacing urea by iodine in the testing for renal function would not have any practical significance if there were not a simple method, suitable for the clinic, of determining the level of iodine in blood and in urine. Several methods for iodine determination were tried by me after the patients had taken different quantities of iodine salts

First of all, I applied incineration methods, in which destruction of the organic substance was obtained by melting with a salt mixture. This method is founded on the classic principle which Rabourdin described in 1850. Many modifications of it have been recommended. After the incineration, the iodine content was determined by titrimetric, gravimetric or colorimetric means. If one wishes to determine the very small quantities of iodine which are normally present in the whole blood (6 to 13 micrograms per hundred cubic centimeters), the method of the Swiss chemist Fellenberg may be used. With this method even 0.1 microgram can be determined. For determination of the much larger quantities of iodine present in blood and urine after administration of, e. g., 4 Gm of sodium iodide, this method, which involves intensive manipulation, is far too sensitive and therefore unsuitable. For more detailed particulars, I refer the reader to the article of Veil and Sturm²⁴. After 4 Gm of sodium iodide has been taken, there is in the blood about 7 to 12 mg of iodine per hundred cubic centimeters, and in the urine, 30 to 700 mg. Incineration methods are suitable to determine these quantities, but they take much time. Besides, a part of the iodine sometimes evaporates at oxidation temperature. A method in which incineration is dispensed with is based on absorption of the alkali iodide by acetone. The acetone is distilled off. The iodide is oxidized with potassium permanganate into iodate. After this it is titrated with a thio-solution. This acetone method, which, at my request, a chemist applied in a number of cases, is so complicated that in my opinion it cannot be recommended for clinical use. For instance, ether extracts of the fat from the dry substance are needed after

24 Veil, W. H., and Sturm, A. *Deutsches Arch f. klin. Med.* **147** 166, 1925

the acetone has been distilled off. Sometimes the so-called "salt error" may make it impossible for more than 50 per cent of the iodine to be shaken out if one does not take precautionary measures.

Therefore, I asked the firm of Hellige to make for the most used colorimeters a special glass slide, with which a content of 7 to 12 mg of iodine per hundred cubic centimeters in solutions (blood, urine) can be determined as accurately as possible. When urine was diluted so that the concentration of iodine in the urine reached about the level of that in blood, one glass slide, which had a measuring capacity for iodine of 7 to 12 mg per hundred cubic centimeters, was sufficient for both blood and urine. This new iodine slide containing two colors is one of the best of the whole series of slides which this firm puts on the market. The colors of the extracts agree well with those of the glass slides. Besides, the firm has succeeded in extending the measuring capacity from 7 to 25 mg of iodine per hundred cubic centimeters of solution. The execution of this method does not cause any difficulties and takes little time. It will be described later. As regards accuracy, this simple colorimetric method for determination of the concentration of iodine in blood and urine is undoubtedly inferior to the aforementioned elaborate acetone and incineration methods, but for clinical purposes it appears to be sufficiently accurate. The results obtained with this simple method are so encouraging that I thought it unnecessary to wait with the publication.

Chabamer²⁵ rightly pointed out the fact that the blood caught on sodium oxalate (or sodium fluoride) must be centrifuged at once to prevent diffusion of iodine in the dying erythrocytes. I have often seen evidence that this advice is correct. When I centrifuged a part of the blood at once and waited for spontaneous separation of the oxalated plasma in the other part, I found by comparison that the erythrocytes can hold 25 to 30 per cent of the plasma iodine. To extract this requires more complicated measures than to prevent diffusion by centrifuging the oxalated blood at once.

The very good agreement of the iodosecretory index and the ureosecretory index in many cases pleads in favor of this simple iodine determination. If the agreement is less satisfactory, the iodosecretory index matches better with the clinical symptoms than the ureosecretory index. Instances of this are noted in table 2.

Secretion curves for iodine after ingestion of 4 Gm of sodium iodide have shown that the method described is reliable. Only then is it practically certain that during the test period fluctuations of the concentration of iodine in blood and urine remain as slight as possible. This is of very great importance for determination of the secretory indexes.

25 Chabamer, H. *Compt rend Soc de biol* 78 445, 1915

Iodine determinations on blood cannot replace the urea determinations. As has been mentioned, one meets with cases in which, on account of hyperthyroidism or idiosyncrasy to iodine, determination of the iodo-secretory index cannot be made. Determination of the ureosecretory index should in that case be preferred.

As to the method of the urea determination, it must be admitted that there are many reliable ones, but often they are needlessly cumbersome for the clinic, e. g., the xanthidrol method, the urease method and the mercury method. The more simple hypobromite method, which gives sufficiently correct results for the clinic, as was demonstrated by Chabanier, Becher, Schmid and Philwert, has the disadvantage that close attention must always be paid to the air-tight fitting of the rubber bags or rubber stoppers when the tube is filled with fluid and gas. Small leaks may have existed for a long time before being detected. From the clinical laboratories of America the hypobromite methods have been largely discarded, and the urease methods have come into vogue. Newer methods can be compared with film stars. It is for both easier to get in than to get out through the large door. Dodson²⁶ stated justly in an American journal for technicians that the urease methods are time consuming and cumbersome, especially in routine work, in which many determinations are made daily. Dodson described an important simplification, but I pointed out that even with this good improvement the urease methods have many disadvantages as compared with a hypobromite method improved by means of a new ureometer²⁷. In the same article the disadvantages of the old hypobromite methods are pointed out. I have tried to construct this simple ureometer for the hypobromite method in such a manner that the difficulties inherent in the other models are removed. The new ureometer possesses the following advantages: 1. Absence of either rubber bags or rubber stoppers. 2. Enclosure of the involved gas in a purely physical way (atmospheric pressure and salt solution of high specific gravity). This assures reliable results. 3. Simple construction, so that the price is low. 4. Strong construction, so that there is little danger of breaking it.

In the very rare cases in which venipuncture is impossible, the formulas must be calculated by the more complicated micromethods. Only in the hands of chemists or physicians of long chemical training do these micromethods give reliable results. This holds especially with regard to the iodine micromethods.

The calculation of secretory indexes can be done quickly with the aid of certain curves, which, at my request, a mathematician has drawn. However, slide rules appeared to me more practical. As the slide rules

26 Dodson, R. V. *Am. J. M. Technol.* 6: 58, 1940.

27 Peters, J. T. *Am. J. M. Technol.* 6: 160, 1940. (See also note at end of this article.)

put on the market were less suitable for these calculations and in general for the calculations with which a physician has to deal, I have designed a new pocket model. The attainable accuracy is 0.5 per cent, so that it is certainly sufficient for the purpose aimed at.²⁸

After making many experiments, I arrived at the following directions regarding the period of preparation, the procedures for determination of the iodosecretory or the ureosecretory indexes and the determination of diuresis with the aid of the creatinine method. It is needless to say that these directions can be modified and adapted to circumstances in many ways. However, the modifications must not be of such extent that the purpose of the preparation period is missed, namely, to avoid as much as possible great fluctuations of the iodine content or of the urea content of the blood and urine during the period of examination.

For determination of both indexes I advise a period of preparation of five and one-half hours. As to the iodosecretory index, one should first make sure that there are no contraindications to the use of iodine (hyperthyroidism, idiosyncrasy to iodine, etc.). When there are none, the use of medicine should be avoided on the day of the test to prevent a possible disturbance of the color reactions in the iodine determination. Especially should acids or medicine from which acids are liberated be avoided. I observed this in the case of a patient who in ordinary circumstances tolerated sodium iodide well. One day, on account of a rheumatic complaint, he had taken some sodium salicylate shortly before taking the sodium iodide. Nausea and vomiting followed. Probably salicylic acid from the sodium salicylate liberated iodine from the iodides. This iodine may irritate the mucous membrane of the stomach by dilating the vessels and increasing the secretion. Care should be taken that no chloroform (to combat growth of bacteria) is added to the urine, because in this method chloroform is used as a means of extraction for iodine.

At the beginning of the preparation period the patient should urinate, trying to empty the bladder completely. The time of urinating should be noted accurately and the urine should be discarded. At intervals of half an hour he should take 0.5 Gm of sodium iodide (e.g., two tablets of 250 mg each dissolved in 15 cc of water) until eight such doses (4 Gm) have been taken. A half or whole peppermint tablet may be added to each dose to mask the flavor. If by mistake or on account of vomiting only 3 Gm has been taken, the test can still be carried out, for I have observed that after ingestion of 3 Gm the color reaction is sufficiently strong to finish the test. However, if more than 1 Gm is vomited it is advisable to repeat the test, for the secretion by the kidneys forms only a part of the iodine secretion. The iodine is removed in many ways. If necessary, defecation should

²⁸ See note at end of article

precede the preparation period, for defecation during the test is to be avoided on account of a possible loss of urine. Within the first two hours of this preparation period a meal may be taken with (at most) 50 Gm of meat or fish and (at most) 100 cc of fluid. (Neither coffee nor tea should be taken, on account of the diuretic action of these substances.) When 4 Gm of sodium iodide in doses of 0.5 Gm at intervals of half an hour has been taken, one should wait two hours before beginning the test proper. However, the patient should continue to drink 15 cc of water every half hour in order to avoid as much as possible greater fluctuations in diuresis during the test proper.

Two hours after the last dose of sodium iodide has been taken, the test proper begins. At this time the patient should urinate, trying to empty the bladder completely. The time should be noted accurately, and the urine should be kept only if one intends to apply the creatinine method to determine the diuresis. Should the patient be unable to retain the urine during five and one-half hours, he is allowed to urinate more than once during the preparation period. The specimens are accurately collected and are added to and mixed up with the specimen taken at the beginning of the test period. Half an hour after the beginning blood is taken, and half an hour later the patient urinates again, trying to empty the bladder completely. This urine is always kept and measured. The time of urinating at the beginning and at the end of the test period is accurately noted. If the creatinine method is not used, the specimen taken at the beginning of the test period is to be discarded.

1 *Determination of the Weight of the Renal Parenchyma*—Note the body height in centimeters, indicated as L . For patients over 18 years of age, the weight of the renal parenchyma is indicated as $N = 1.4 \times L$. For patients under 18 years of age, the weight of the renal parenchyma can be read from chart 2.

2 *Determination of the Minute Volumes*— M^1 is assumed to be the minute volume of the urine voided during the preparation period, and M , the minute volume of urine voided during the test period.

a *Without the Creatinine Method*. Suppose that the test period lasts q minutes. After this the patient voids p cc of urine. The minute volume for the test period is then expressed as $M = \frac{p}{q}$ cc.

b *With the Creatinine Method*. The preparation period lasts s minutes. After this the patient voids r cc of urine. The minute volume for the preparation period is $M^1 = \frac{r}{s}$ cc.

I have called the minute volume for the test period M , the concentration of creatinine in the urine for the same period K and the volume of the urine, read with similarity of color in a Duboscq type of colorimeter, v . The same values for the urine of the preparation period

I have called M^1 , K^1 and v^1 When using the Zeiss-Ikon colorimeter (constructed for determination of the level of blood sugar), one calculates $M = \frac{K^1 \times M^1}{K}$ When using a Duboscq type of colorimeter, one calculates $M = \frac{v \times M^1}{v^1}$

3 *Determination of the Iodosecretory Index (I I)*—a Examination of the Urine Measure 0.5 cc of urine and place it in a measuring glass, in which previously 10 cc of chloroform has been put Add 3 cc of 4 per cent potassium nitrite solution and 3 cc of normal hydrochloric acid Shake Filter the colored chloroform solution through a dry filter in the tube or wedge of the colorimeter, in which the aforementioned "iodine sliding glass" has been placed Various models of colorimeters can be used with different models of iodine sliding glasses When, with similarity of color, one reads from a table (accompanying the sliding glass) p mg of iodine in 100 cc of chloroform, then the urine contains $\frac{200 \times p}{10} = 20 \times p$ mg of iodine per hundred cubic centimeters = Iu If the color turns dark violet, add 10 cc more of chloroform, in order to make the reading easier Then the denominator 10 in the calculation should be replaced by 20

b Examination of the Blood Twenty-eight to 30 cc of oxalated blood is required By means of a thicker venipuncture needle blood is allowed to run quickly into a glass cylinder on sodium oxalate After thorough shaking, it is poured at once into two or four centrifugal tubes of such measurements that one has at one's disposal after centrifuging 15 cc of oxalated plasma Centrifuge as soon as possible (A centrifugal tube filled with 15 cc of oxalated blood produces 8 or 10 cc of oxalated plasma when centrifuged in a strong centrifuge for ten minutes) Add to 15 cc of oxalated plasma an equal part of 20 per cent trichloroacetic acid Shake thoroughly Pour this mixture into a large filter, measure off 20 cc of the filtrate (containing 10 cc of plasma) This 20 cc of filtrate is placed in a measuring glass into which previously 10 cc of chloroform has been put Add 3 cc of 4 per cent potassium nitrite solution and 3 cc of normal hydrochloric acid Shake Filter the colored chloroform solution through a dry filter in the wedge or tube of the colorimeter, in which the aforementioned iodine sliding glass has been placed When, with similarity of color, one reads from the accompanying table q mg of iodine in 100 cc of chloroform then the blood contains $\frac{10 \times q}{10} = q$ mg of iodine per hundred cubic centimeters = Ib

4 *Determinations of the Ureosecretory Index*—a Urine Test (with the aforementioned ureometer) Suppose that 0.5 cc of urine has been diluted with water to 50 cc and of this diluted urine 10 cc has been used for the test as described in the instructions accompanying

each ureometer and also in an article previously published²⁷ When one reads on the ureometer a cc of nitrogen, then the urine contains $27 \times \frac{a}{0.1}$ Gm of urea per liter = C , or $126 \times a$ milligrams of urea nitrogen in 100 cc of urine = U

(The albumin should be removed from albuminous urine before the test is made)

b Blood Test (with the aforementioned ureometer) About 15 cc of oxalated blood is recommended, although the ureometer can be used with much less blood Add to it, in a glass cylinder, equal parts of 20 per cent trichloroacetic acid Shake thoroughly Pour this mixture into a filter As one wishes to use 5 cc of blood, 10 cc of the filtrate should be mixed with the bromite solution in the ureometer according to the elaborate directions accompanying the apparatus When one reads a cc of nitrogen, the blood contains $27 \times \frac{a}{5}$ Gm of urea per liter = Ur , or $25 \times a$ milligrams of urea nitrogen in 100 cc of blood = B

If there was less than 10 cc of filtrate, also half the quantity of the filtrate will consist of blood, and the number expressing this half replaces 5 in this comparison

With these and the aforementioned data the formulas described can be easily calculated

Withdrawal of 15 cc of blood for the determination of the ureosecretory index or of 30 cc of blood for the determination of the iodosecretory index is not harmful for patients who are not weakened by serious complications In my experience with numerous patients, I never saw any harm done Osgood²⁹ calculated that after withdrawal of 50 cc of blood in ten days, *even if no regeneration of blood occurs*, but only the blood volume returns to its previous value, the lowering of the hemoglobin percentage is less than the normal daily variation

As to the preparing of oxalated blood for these examinations, I recommend Osgood's method of making a stock of tubes, each containing 2 mg of dry powdered sodium oxalate per cubic centimeter of blood For example, in the tubes for 15 or 30 cc of blood, one measures, with a buret, 1.5 or 3 cc respectively of a 2 per cent solution of sodium oxalate and evaporates the water in an oven

The protein-free filtrate should always be prepared as soon as possible after the withdrawal of the blood It will keep well for twelve hours if placed directly in an ice box For the urea determination, the preparation of the protein-free filtrate with trichloroacetic acid may be replaced by the tungstic acid method, but the latter is more cumbersome and is no better for this special case

²⁹ Osgood,²¹ p 461

It is not advisable to subtract the ammonia nitrogen from the urea nitrogen of the urine (as has often been recommended), because ammonia is formed from urea in the kidney

To detect errors in the technical execution, it is recommended to take two specimens of urine at the same test and to repeat the test if the results disagree more than 30 per cent. However, by this method an error is not detected if it is present only in calculation of the blood urea nitrogen. Therefore a repetition of the test within a week seems to me better.

If one wishes to judge at the same time of the quantity of blood urea with a nitrogen-deficient diet, meat, fish, eggs and milk should be forbidden on the day of examination. The same holds when a relative oliguria with regard to urea is suspected and there is no opportunity to determine the iodosecretory index, so that determination of the ureosecretory index is the only test left. In such cases the supply of fluid should be heightened a little. When there is no reason or no opportunity to apply the creatinine method for measuring the diuresis, then, of course, the period of preparation can be shorter, etc.

JUDGMENT OF THE RESULTS OF THESE TESTS

Both indexes, whose object is to determine the efficiency of the kidney tissue in the removal of an iodine salt or urea from the blood, can give only momentary pictures of the renal function. These momentary pictures like, e. g., roentgenograms of the kidneys, should be compared with the results of anamnestic, clinical, physical, chemical and microscopic examinations.

The slide rules, ureometers, slide glasses and colorimeters mentioned in this article are to be distributed by Eugene Baehr and Sons, 251 Fourth Avenue, New York.

AN EXPERIMENTAL STUDY OF RECIPROCATING RHYTHM

DAVID SCHERF, M D

NEW YORK

As evolution proceeded, the muscular connection between auricles and ventricles gradually diminished. In the piscine heart, junctional fibers are present and conduct equally well in either direction at the whole circumference of the auriculoventricular border. In the amphibian heart, some parts of the junctional tissue conduct better than others, in some sections, reversed, or ventriculoauricular, conduction is even more rapid than normal, or auriculoventricular, conduction. Differences in conductivity are even more pronounced in the reptilian heart, and a reduction in the amount of conduction tissue has occurred.¹ Differentiation and specialization are still more evident in the avian heart and in the mammalian heart the relatively small auriculoventricular conduction system furnishes the only morphologic connection between auricles and ventricles. Thus, functional differentiation may be assumed to have preceded anatomic alteration and reduction.

A second communication between auricles and ventricles in man has been suggested as an atavistic, inherited anomaly occurring on rare occasions. Since each phylogenetic stage is repeated in ontogenesis, such observations become comprehensible.² This second junction between auricles and ventricles has been assumed by virtue of an analysis of certain peculiar electrocardiograms recorded in man, anatomic confirmation has not been secured.

From the New York Medical College and the Flower and Fifth Avenue Hospitals. Aided by a grant from the Ella Sachs Plotz Foundation.

1 von Skramlik, E. Ueber die anatomische Beschaffenheit der Ueberleitungsgebilde des Kaltbluterherzens, *Ztschr f d ges exper Med* **14** 246, 1921, Ueber die Beziehungen zwischen der normalen und rucklaufigen Erregungsleitung beim Froschherzen, *Arch f d ges Physiol* **184** 1, 1920.

2 Kent, A. F. S. Researches on the Structure and Function of the Mammalian Heart, *J Physiol* **14** 233, 1893. Holzmänn, M., and Scherf, D. Ueber Elektrokardiogramme mit verkürzter Vorhof-Kammer-Distanz und positiven P-Zacken, *Ztschr f klin Med* **121** 404, 1932. Wolferth, C. C., and Wood, F. C. The Mechanism of Production of Short P-R Intervals and Prolonged QRS Complexes in Patients with Presumably Undamaged Hearts. Hypothesis of an Accessory Pathway of Auriculo-Ventricular Conduction (Bundle of Kent), *Am Heart J* **8** 297, 1933. Scherf, D., and Schonbrunner, E. Beiträge zum Problem der verkürzten Vorhofkammerleitung, *Ztschr f klin Med* **128** 750, 1935.

One of the outstanding problems of auriculoventricular conduction still subject to discussion is the function of, and conductivity in, the auriculoventricular node. Its position in the center of the heart, almost inaccessible to experimental investigation, is one of the important reasons for the meager knowledge regarding its physiology. The present experimental study was undertaken with the purpose of investigating a remarkable disturbance of cardiac action in which mainly the auriculoventricular node itself seems to be involved.

After the application of a series of electrical stimuli to the heart of the frog or the fish, Mines noticed a peculiar disturbance of cardiac rhythm.³ Auricles and ventricles contracted alternately, and it could be shown that a wave was conducted in a circle going from the auricles to the ventricles and then back from the ventricles to the auricles and so forth. This disturbance was explained by the assumption of a slight difference in the length of the refractory period in certain parts of the junctional tissue between auricles and ventricles. The stimulus thus traveled in one part of this tissue from the auricle to the ventricle and in another from the ventricle to the auricle.

An observation of a similar disturbance in man was reported and correctly interpreted by White.⁴ A series of additional observations followed.⁵ Similar but dubious cases may be found in the literature prior to the invention of the electrocardiograph.⁶ In all these cases an auriculoventricular rhythm existed. Sometimes, without any other

3 Mines, G. R. On Dynamic Equilibrium in the Heart, *J. Physiol.* **46** 349, 1913.

4 White, P. D. A Study of Atrioventricular Rhythm Following Auricular Flutter, *Arch. Int. Med.* **16** 517 (Oct.) 1915, The Bigeminal Pulse in Atrioventricular Rhythm, *ibid.* **28** 213 (Aug.) 1921.

5 (a) Bishop, L. F. Specific Action of Atropin in Relieving Certain Irregularities of Heart Beat, *J. A. M. A.* **77** 31 (July 2) 1921. (b) Blumgart, H. L., and Gargill, S. L. Reciprocal Beating of the Heart, *Am. Heart J.* **5** 424, 1930. (c) Cutts, F. B. Reciprocal Rhythm in a Patient with Congenital Heart Disease, *ibid.* **14** 717, 1937. (d) Dock, W. The Reciprocal Rhythm, *Arch. Int. Med.* **41** 745 (May) 1928. (e) Drury, A. N. Paroxysmal Tachycardia of A-V Nodal Origin, Exhibiting Retrograde Heart Block and Reciprocal Rhythm, *Heart* **11** 405, 1924. (f) Gallavardin, L., and Gravier, L. Bradycardie nodale permanente, étude du rythme atrio-ventriculaire, *Arch. d. mal. du cœur* **14** 71, 1921. (g) Gravier, L., Froment, R., and Guiran, J. B. Brady-arythmie sinusale avec automatisme ventriculaire permanent et "reciprocal rhythm," *ibid.* **32** 622, 1939. (h) Reid, W. D. Permanent Bradycardia Following Diphtheria, *Am. Heart J.* **5** 524, 1930. (i) Samojloff, A., and Tschernoff, A. Reziproker Herzrhythmus beim Menschen, *Ztschr. f. d. ges. exper. Med.* **71** 768, 1930.

6 Wenckebach, K. F. Beiträge zur Kenntnis der menschlichen Herztätigkeit V. Ueber Dissoziation der Tätigkeit beider Vorkammern, *Arch. f. Physiol.*, 1906 p. 297. Muskens, L. J. I. Genesis of the Alternating Pulse, *J. Physiol.* **36** 104, 1907.

obvious cause, during carotid pressure or during digitalis therapy backward conduction occurred from the auriculoventricular node to the auricle, occasionally this was delayed to such a degree that the auricles

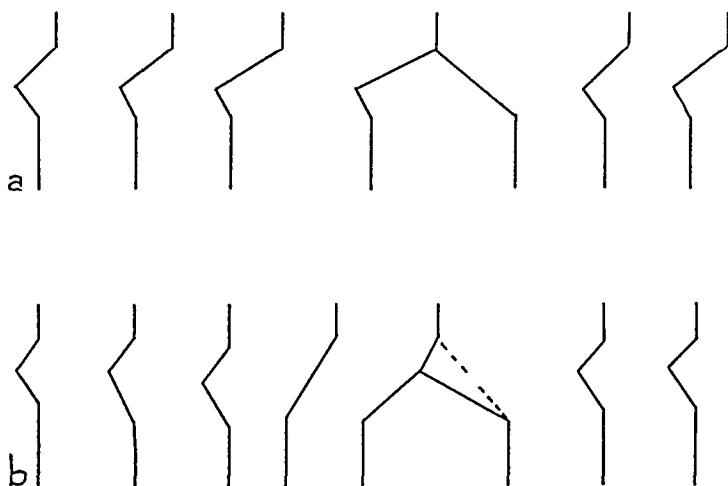


Fig 1—(a) The mechanism of a reciprocating beat during auriculoventricular rhythm with gradually prolonged reversed conduction (b) The mechanism of a return extrasystole after a reversely conducted ventricular extrasystole during auriculoventricular rhythm

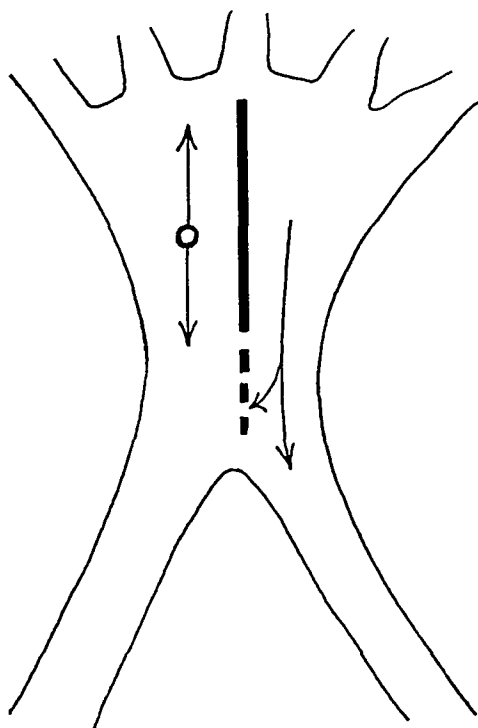


Fig 2—The drawing indicates the longitudinal functional dissociation in the auriculoventricular node (heavy line in the center) during auriculoventricular rhythm. The part of the conduction system just above the bifurcation may be employed by both the return extrasystole and the preceding, initiating beat

contracted considerably later than the ventricles and an inverted P wave appeared some time after the QRS complex. This was followed by a new ventricular systole. It was assumed that the stimulus originating in the auriculoventricular node was reversely conducted from the node to the auricle and then returned once again to the ventricle, thus causing a second ventricular systole (reciprocating beat). The schematic drawings in figures 1 *a* and 2 explain this mechanism. In the cases reported, the auriculoventricular rhythm was usually the result of a lesion in the sinus node. However, *single* reciprocating (or reciprocal) beats occurred in the majority of the clinical observations, whereas Mines described a *continuous* reciprocating rhythm. In only 1 case⁵¹ were tracings taken, which suggest, but do not prove, the possibility of a short period of reciprocating rhythm.

There have been no experimental studies concerning this arrhythmia, but a similar disturbance has been described in dogs, an auriculoventricular rhythm appeared after a clamp was applied to the sinus node.⁷ Electrical stimulation was then employed to produce a series of ventricular extrasystoles. Usually they were conducted backward to the auricle. Frequently the last extrasystole of a series which was conducted backward to the auricle "returned" and again reached the ventricle, thus a premature ventricular systole followed (fig 1 *b*). (The new premature abnormal beat has been called "return extrasystole" [reciprocating beat]). Some observations indicated that the last ventricular extrasystole reversely conducted turned back in the auriculoventricular node and once more reached the ventricle. The observation that the PR interval of the return extrasystole became shorter as the length of the preceding RP interval became longer seemed to suggest that at least a part of the pathway was used twice by the stimulus.

EXPERIMENTAL OBSERVATIONS

The experiments were performed on dogs whose hearts had been exposed by opening the chest wall and the pericardium. Both vagus nerves were cut in the neck. Ether or pentobarbital sodium anesthesia was used. An auriculoventricular rhythm was induced by compressing the sinus node with three or more clamps, as well as by clamping the arteries of the sinus node. In some experiments the action of the sinus node was inhibited by cooling. Any one who has tried to eliminate the action of the sinus node experimentally knows how difficult this task may be, since aberrant parts of it or variations in its position are not uncommon. For the purpose of these experiments it was important to secure that form of auriculoventricular rhythm in which the auricles contracted *after* the ventricles. This was difficult, frequently the more common type appeared, and all chambers contracted simultaneously. In some experiments the injection of 0.01 to 0.02 Gm

⁷ Scherf, D., and Shookhoff, C. Experimentelle Untersuchungen über die "Umkehr-Extrasystole" (Reciprocating Beat), *Wien Arch f inn Med* **12** 501, 1926.

of quinidine sulfate was necessary to prevent ventricular fibrillation occurring after application of rapid electric stimuli to the ventricles. Often this amount of quinidine impaired the reversed conduction from the auriculoventricular node to the auricle sufficiently to give the form of auriculoventricular rhythm desired, that is, the P wave following the QRS complex. If this form of rhythm was present, stimulation of the left vagus nerve with a weak faradic current frequently produced prolongation of the RP interval.

In 11 of 28 experiments, return extrasystoles were observed. The experiments may be divided into two groups. In one, the abnormal rhythm was evoked by fatiguing the conduction system with many extrasystoles following each other at short intervals. In the other, the abnormal rhythm appeared during stimulation of the left vagus nerve with a weak faradic current.

In figures 3 *A* and *B* the application of induction shock stimuli is marked at the top by an electrical signal. Then follow the contractions of the right auricle and the right ventricle recorded by mechanical tracings. The time record in these tracings amounts to 0.02 second. In all others it is 0.04 second.

The auriculoventricular rhythm recorded in figure 3 *A* appeared after the sinus node was clamped. The mechanical tracings show that the auricles contracted after the ventricles, and in the electrocardiogram an inverted P wave is visible after the QRS complex. Observation for a period of five minutes did not reveal any change of rate or rhythm. At this time auricular extrasystoles were produced, and eight of them were conducted to the ventricle. Immediately thereafter, the auriculoventricular rhythm reappeared. Prior to the stimulation of the auricle, the P wave was visible 0.04 second after the beginning of the initial complex, in the first postextrasystolic beat after the extrasystoles it appeared after 0.10 second. It was followed after 0.11 second by a slightly aberrant premature beat (return extrasystole). Then an alteration of the reversed conduction from the auriculoventricular node to the auricle ensued because one RP interval measuring about 0.05 second alternated with the one following which measured approximately 0.09 second. Every beat with the longer RP interval was followed by a return extrasystole. After the appearance of six to eight of these extrasystoles the alternation of the reversed conduction stopped, and the auriculoventricular rhythm showed constantly the same short RP interval as before the extrasystoles. A new series of auricular extrasystoles was released five times, and the same disturbance always followed. The diagnosis of a return extrasystole in this tracing was based on the fact that it appeared only after those artificial auricular extrasystoles which caused a prolongation of the RP interval and disappeared as soon as this interval became shorter.

In another experiment (fig 3 *B*), clamping the sinus node caused an auriculoventricular rhythm in which the auricles and ventricles contracted practically at the same time (first beat from the left). Four induction shocks caused three ventricular extrasystoles, one of them was conducted in a retrograde manner to the auricle as shown by the suspension tracing. In the first postextrasystolic auriculoventricular beat the auricles contracted 0.02 second after the ventricles, in the next auriculoventricular beat the auricles were activated 0.08 second later.

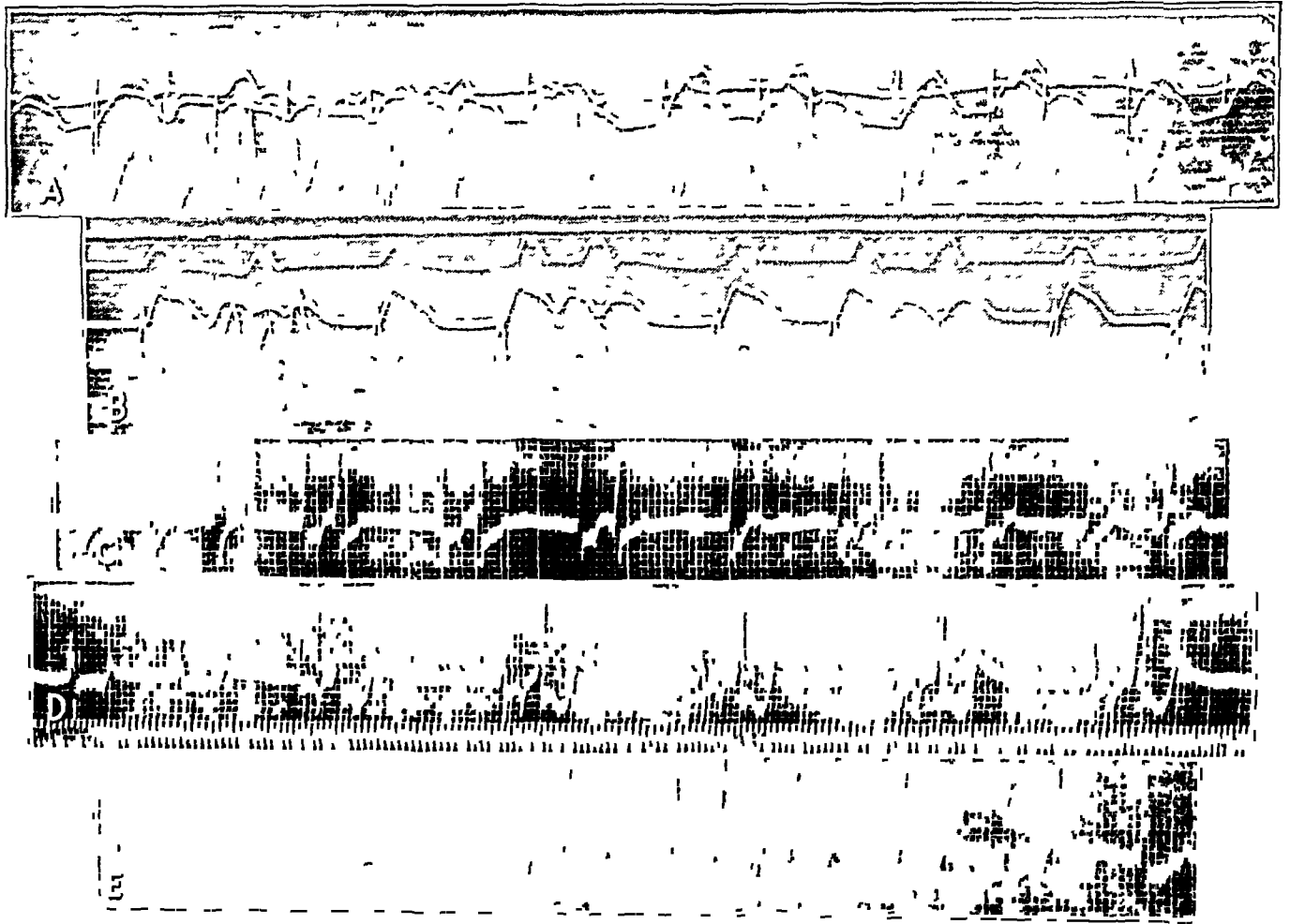


Fig 3—*A*, the first two beats show an auriculoventricular rhythm, after a series of auricular extrasystoles an alternation of the reversed conduction from the node to the auricle follows. A return extrasystole appears after every beat with a prolonged RP interval. *B*, the first beat shows an auriculoventricular rhythm. After three ventricular extrasystoles an alternation of the length of the RP interval appears with two return extrasystoles after the beat with the longer RP interval. *C*, the first three complexes show an auriculoventricular rhythm with an inverted P wave, just visible after the QRS complex. Faradic stimulation of the left vagus nerve causes a prolongation of the RP interval and initiates return extrasystoles. *D*, bigeminal rhythm due to return extrasystoles during stimulation of the vagus nerve. *E*, "interpolated" return extrasystoles without disturbance of the auriculoventricular rhythm.

than the ventricles, although not late enough to cause a clearcut P wave after the initial complex. The mechanical tracing, however, permitted measurement of the RP interval. In the following cycles one sees again the continuous alternation of a short and a long RP distance in the auriculoventricular beats as in figure 3 *A*. Here again, a return extrasystole appeared after every beat with a longer RP distance. The PR interval of this beat was 0.24 second long. In this experiment, however, the return extrasystole was again conducted backward to the auricle with a conduction time of 0.14 second and was followed by a second return extrasystole whose auriculoventricular conduction time was 0.13 second. The alternation in length of the RP interval as well as the return extrasystole disappeared after four or five cycles. Here also, renewed stimulation of the ventricle, repeated three times, initiated the same picture. The diagnosis of a return extrasystole not only was confirmed by the analysis of the electrocardiogram and the mechanogram but was substantiated by the fact that the peculiar trigeminal groups invariably appeared if the RP interval of the auriculoventricular beats was sufficiently prolonged but appeared at no other time.

These experiments showed that under certain conditions a bigeminal and a trigeminal rhythm may be due to return extrasystoles.

In the second group of experiments an auriculoventricular rhythm was evoked by compressing the sinus node and by clamping its arteries. If after this procedure an auriculoventricular rhythm appeared in which the excitation of the auricle occurred immediately following the excitation of the ventricle, the left vagus nerve was stimulated with a weak faradic current. In this manner one usually succeeds in producing a reversed block between the auriculoventricular node and the auricle, as demonstrated by the appearance of an RP interval.⁸

The first three beats in figure 3 *C* show a regular auriculoventricular rhythm with an inverted P wave just visible after the initial ventricular complex. Stimulation of the left vagus nerve prolonged the RP distance to about 0.12 second. The first three auriculoventricular beats and the fifth beat are followed by a return extrasystole with a PR interval of about 0.12 second. The RP interval of the fourth beat is shorter, and therefore it is not followed by a return extrasystole. At the end of the tracing two sinus beats with inverted P waves and a PR interval of 0.11 second appear, this indicates that the clamps did not succeed in completely destroying the action of the sinus node. The "escape" of sinus beats during the auriculoventricular rhythm induced by cooling the sinus node has been observed and discussed by Lewis and White.⁹

⁸ Lewis, T. The Effect of Vagal Stimulation upon Atrioventricular Rhythm, *Heart* 5 247, 1914.

⁹ Lewis, T, and White, P. D. The Effects of Premature Contractions in Vagotomised Dogs, with Especial Reference to Atrioventricular Rhythm, *Heart* 5 335, 1914.

Repeated stimulation of the left vagus nerve always resulted in the same disturbance. As in the previous experiment (fig 3 *B*), the abnormal beats appeared exclusively and regularly as soon as the RP interval was sufficiently prolonged.

In another experiment (fig 3 *D*), the auriculoventricular rhythm appeared after the artery of the sinus node was clamped and after the application of three clamps to the sinus node itself. Auricles and ventricles contracted simultaneously. After the first two beats the left vagus nerve was stimulated. Immediately a deep inverted P wave appeared, about 0.11 second after the initial complex. After 0.12 second it was followed by a slightly aberrant return extrasystole. It is interesting to note that this return extrasystole appeared at a time when the T wave of the auriculoventricular beat had not as yet begun. In this experiment, as well as in others, continuous bigeminal rhythm appeared whenever the vagus nerve was stimulated, and it disappeared immediately when vagal stimulation was discontinued. Stimulation of the vagus nerve with a weaker faradic current caused a shorter RP interval and therefore failed to release the return extrasystoles.

The question concerning the pathway over which the stimulus returns cannot as yet be definitely answered. The evidence of older experiments seemed to suggest that the return takes place in the upper part of the auriculoventricular node.⁷ This possibility was originally considered by Drury. The sharp difference in the histologic structure between the auricular and the ventricular part of the auriculoventricular node may warrant the assumption of a difference in function. However, it seems inconceivable that the stimulus conducted from the auriculoventricular node back to the auricle would on its return to the ventricle utilize exactly and exclusively the same path. One must assume that at least the upper part of the conduction system is divided longitudinally into two paths (fig 2). Many junctional fibers exist between the auriculoventricular node and the auricle, and, as conduction within the auriculoventricular node itself appears to be a complicated process, this functional dissociation may well occur.

The fact that, at least in part, different pathways are utilized was shown by other observations. Thus, in figure 3 *E*, an auriculoventricular rhythm existed, initiated by clamping the sinus node and its arteries. During stimulation of the left vagus nerve with a weak faradic current an inverted P wave became visible between the QRS interval and the T wave, usually it appeared 0.12 second after the beginning of the R wave. On three occasions the RP distance was longer than 0.12 second, and a return extrasystole followed. The distances between the auriculoventricular beats directly following each other at the beginning of the tracing vary only from 0.58 to 0.60 second. The distances

between the last auriculoventricular beat before and the first after the return extrasystoles in figure 3 *E* measure 0.68, 0.67 and 0.72 second. If one measures 0.60 second back from the first postextrasystolic auriculoventricular beat, a point preceding the retrograde conducted P wave is always reached. Formation of the stimulus for the auriculoventricular beat which follows the return extrasystole must therefore start at a time when the preceding auriculoventricular beat has not as yet reached the auricle, probably when this stimulus has just left the auriculoventricular node. But on its way down to the ventricle the return extrasystole itself does not disturb the auriculoventricular center. Either it is conducted downward by another path, or it does not break into the auriculoventricular center because the latter is "protectively blocked."

The shortening of the RP interval in the first auriculoventricular beat after the return extrasystole and the slight delay of the first postextrasystolic ventricular complex are consequences of the slower conduction in the bundle of His below the auriculoventricular node. At least a part of this section of the auriculoventricular system conducted three stimuli within a short period. The validity of this explanation is supported by the following facts. If the P-P distances in figure 3 *E* are measured, only small variations are found, since the auriculoventricular center is not disturbed by the return extrasystole. Slight disturbances of the interventricular intervals of the auriculoventricular beats and of the RP distances are produced by conduction disturbances in the lower parts of the auriculoventricular system.

This undisturbed action of the auriculoventricular center was however, frequently absent. The failure of stimuli conducted from the auricle to the ventricle to disturb the action of an auriculoventricular center has been noted by Lewis and White⁹ and Rothberger and Winterberg.¹⁰

COMMENT

These experiments show that under certain conditions a return extrasystole (or reciprocating beat) may occur in dogs and present the picture of a continuous bigeminal or trigeminal rhythm. The "method of extrasystole," which was instrumental in producing a reciprocating rhythm in Mines's experiments with the hearts of fish and of frogs, has been useful in experiments on mammalian hearts which have a small auriculoventricular connection. The method of inducing return extrasystoles in an auriculoventricular rhythm by vagal stimulation

10 Rothberger, C. J., and Winterberg, H. Ueber Extrasystolen mit kompensatorischer Pause bei Kammerautomatie und über die Hemmungswirkung der Extrasystolen, *Arch f d ges Physiol* **146** 385, 1912.

is an imitation of the clinical experience in which the same disturbances are manifested during carotid pressure or digitalization in patients with an auriculoventricular rhythm. With both methods, the RP interval of the auriculoventricular beats is prolonged, and thus the essential condition for the appearance of the return extrasystole is present. The similarity between the clinical observations and experimental tracings is striking. At present it is not possible to decide whether the prolongation of the RP interval alone is sufficient to cause the appearance of return extrasystoles. It is probable that functional longitudinal dissociation of the upper part of the auriculoventricular system is not always present but results from the extrasystoles or vagal stimulation. Once this dissociation develops, the return extrasystole can always appear provided the RP interval has a certain length, otherwise the return extrasystole would not be conducted to the ventricle by the lower part of the auriculoventricular system which is still refractory and in which no longitudinal dissociation exists.

Functional longitudinal dissociation in the small auriculoventricular system of the mammalian heart must be assumed, since the second utilization of the same pathway within a short time seems impossible in the light of present knowledge.

It is interesting to note that in experiments on the turtle's heart, using small strips of ventricular tissue, which is, of course, much less differentiated than ventricular tissue from the mammalian heart, Schmitt and Erlanger¹¹ found the phenomenon of reentry under certain conditions. They called it *opisthodomia*. A stimulus applied to the left end of the muscle strip spread to the right and returned to the left end. Reentry appeared whenever conduction in a small pathway was possible in only one direction (unidirectional block) and the adjacent fibers were able to conduct in both directions. Older experiments also supported the idea of the occurrence of multiple pathways with varying powers of conduction in the normal direction.¹² The same phenomenon was observed in the experiments described in this paper. The RP interval occasionally was longer than the PR interval of the following return extrasystole.

The alternating retrograde conduction in figures 3 *A* and *B* is also of interest. Alternation of the normal auriculoventricular conduction

11 Schmitt, F. O., and Erlanger, J. Directional Differences in the Conduction of Impulse Through the Heart Muscle and Their Possible Relation to Extrasystolic and Fibrillary Contractions, *Am J Physiol* **87** 326, 1921.

12 Engelmann, T. W. Die Blatterschicht der elektrischen Organe von Raja in ihren genetischen Beziehungen zur quergestreiften Muskelsubstanz, *Arch f d ges Physiol* **57** 149, 1894. Erlanger, J. Further Studies on the Physiology of Heart Block, *Am J Physiol* **16** 160 1906.

has been observed on rare occasions, for example, during asphyxia¹³ or during a fast tachycardia¹⁴ Different degrees of reversed block were included among the clinical observations of Drury^{5e}

The experiments reported suggest that premature ventricular contraction may be caused by a reentry mechanism Although this has been seen up to the present time only during an auriculoventricular rhythm, the idea cannot be dismissed that a similar disturbance in a peripheral part of the ramifications of the auriculoventricular system may cause the same mechanism when unidirectional block and delayed conduction are present The reentry mechanism may be situated in the right or in the left ventricle and may initiate the formation of ventricular extrasystoles during sinus rhythm Certain observations¹⁵ seem to show, however, that, at least under some conditions, extrasystoles are evoked by an abnormal formation of stimuli independent of a disturbance of the conduction of the stimulus

A longitudinal dissociation in the auriculoventricular conduction system with faster conduction in one bundle branch may explain tracings with the syndrome of Wolff, Parkinson and White¹⁶ (Cooke and White, personal communication)

SUMMARY

An auriculoventricular rhythm was produced in dogs' hearts *in situ*, functional longitudinal dissociation appeared after the conduction system was fatigued by means of a series of extrasystoles or during stimulation of a vagus nerve In this stage return extrasystoles (reciprocating beats) appeared whenever the RP interval of the auriculoventricular beats was prolonged The experiments prove that under certain conditions bigeminal or trigeminal rhythm may be due to a reentry mechanism

13 Lewis, T, and Mathison, G C Auriculo-Ventricular Heart-Block as a Result of Asphyxia, *Heart* **2** 47, 1910

14 Lewis, T, Feil, H S, and Stroud, W D Some Effects of Rhythmic Stimulation of the Auricle, *Heart* **7** 247 1920 Kaufmann, R, Rothberger, C J, and Kauf, E Ueber die Entstehungsarten allorhythmischer Ventrikeltätigkeit bei Vorhofflattern, *Ztschr f d ges exper Med* **51** 766, 1926

15 Scherf, D Ueber den Zusammenhang zwischen festgekuppelten Extrasystolen und extrasystolischen Tachykardien, *Ztschr f d ges exper Med* **70** 375, 1930

16 Wolff, L, Parkinson, T, and White, P D Bundle Branch Block with Short P-R Interval in Healthy Young People Prone to Paroxysmal Tachycardia, *Am Heart J* **5** 685, 1930

RELATION OF LIVER FUNCTION TO CIRRHOSIS OF LIVER AND TO ALCOHOLISM

COMPARISON OF RESULTS OF LIVER FUNCTION TESTS WITH DEGREE OF
ORGANIC CHANGE IN CIRRHOSIS OF LIVER, AND WITH RESULTS
OF SUCH TESTS IN PERSONS WITH ALCOHOLISM
WITHOUT CIRRHOSIS OF LIVER

H B CATES, M D
LOS ANGELES

The value of liver function tests remains in doubt. Too frequently the physician who is confronted by a difficult problem in diagnosis has liver function tests made when they are not indicated and is then left in confusion as to what interpretation to place on the results when they have been obtained. In this paper an effort is made to correlate the results of function tests with anatomic changes in the liver. In all except 1 of the cases studied, the diagnosis of cirrhosis of the liver was confirmed by examination with the peritoneoscope¹. In all but 3 instances, a piece of the liver was removed for microscopic examination, which made it possible to compare the results of function tests with the severity of the lesion as determined by the pathologist. Classification of the changes found by the pathologist as chronic or subacute cirrhosis is purely arbitrary. The diagnosis of subacute cirrhosis implies that the disease process has not reached a terminal stage as indicated by the reactions of the tissue to the damaging agent or agents, but the determination of the changes histologically does not measure or enable one to predict the functional capacity of the liver in question. From the therapeutic viewpoint, a patient who as a result of biopsy is found to have subacute cirrhosis still has significant chances of responding to correct management.

The patients studied in this work had the following tests made on them—after biopsy of the liver had been done—determination of total serum proteins and the albumin-globulin ratio, the hippuric acid test, the bromsulphalein test, except for those patients who were jaundiced, and determination of serum cholesterol and cholesterol esters. In a few

From the Department of Medicine of the University of Southern California School of Medicine and the medical service of the Los Angeles County Hospital

1 Service of Dr John Ruddock

instances, the Takata-Aia, galactose tolerance or urobilinogen test was made before biopsy of the liver had been done, but no great importance was attached to the results of these procedures

METHOD

It is not out of place to consider briefly the tests used

Serum Proteins—These substances are important in this problem because one of the most significant alterations in metabolism associated with chronic hepatitis is the disturbance in their formation. Amino acids brought to the liver from the intestine are not converted into serum proteins in adequate amounts, consequently their concentration gradually decreases as the liver tissue is destroyed and its function fails. When the concentration of serum proteins reaches a critical level, edema, and especially ascites, follows. Addis, Poo and Lew² found that during two days of starvation rats lost 20 per cent of the protein from the liver and only 4 per cent of the protein from the kidneys, heart and other organs. The effect of partial hepatectomy on the blood proteins of rats was studied by Chanutin and his associates³. They found that on the first day following operation the blood plasma, fibrin, albumin and globulin were reduced and that by the third day the concentration of fibrin and globulin was above normal and remained so, but that the concentration of albumin was decreased and remained so during the thirty day period of observation. Decreased concentration of serum proteins in association with a diseased condition of the liver was emphasized by Salvesen⁴. He found that serum albumin decreased until it was equal to or less than the globulin fraction. He studied 16 female patients as controls and found their albumin-globulin ratio ranged between 1.26 and 2.00 with an average of 1.62, a similar study of 16 male patients gave ratios between 1.43 and 2.26, with an average of 1.72. His patients who had cirrhosis of the liver were found to have ratios between 0.30 and 0.89. Observations by Foley, Keeton, Kendrick and Darling⁵ led them to state that the decrease of serum albumin in this condition is not the result of mechanical removal, but that serum proteins may pass from the blood into large accumulations of ascitic fluid without altering their concentration in the blood. In a study of patients who had nephrosis, Barker and Kirk⁶ found that there was a daily loss of from 5 to 6 Gm. of protein and that a daily loss of 4 Gm. was accompanied by a reduction in concentration of serum proteins. It has been observed that the albumin-globulin ratio is reversed in patients who

2 Addis, T., Poo, L. J., and Lew, W. Protein Loss from the Liver During a Two-Day Fast, *J. Biol. Chem.* **115** 117-118 (Aug.) 1936

3 Chanutin, A., Hortenstine, J. C., Cole, W. S., and Ludwig, S. Blood Plasma Proteins in Rats Following Partial Hepatectomy and Laparotomy, *J. Biol. Chem.* **123** 247-256 (March) 1938

4 Salvesen, H. A. Variations in Plasma Protein in Non-Renal Conditions, *Acta med. Scandinav.* **72** 113-123, 1929

5 Foley, E. F., Keeton, R. W., Kendrick, A. B., and Darling, D. Alterations in Serum Protein as an Index of Hepatic Failure, *Arch. Int. Med.* **60** 64-76 (July) 1937

6 Barker, M. H., and Kirk, E. J. Experimental Edema in Dogs in Relation to Edema of Renal Origin in Patients, *Arch. Int. Med.* **45** 319-346 (March) 1930

have nutritional edema, and under these circumstances Liu and his associates⁷ found that the addition of 28 Gm of protein would reestablish the normal level. Thompson, McQuarrie and Bell⁸ studied a 2 year old girl who had an intractable edema and who was not benefited by a protein intake of from 25 to 35 Gm per kilogram of body weight. Her urine contained no albumin. At autopsy she was found to have primary atrophy of the liver and a normal heart and kidneys. They concluded that the injured liver was incapable of fabricating the needed serum albumin and globulin.

Hippuric Acid—The hippuric acid test of Quick⁹ is a measure of the capacity of the liver to detoxify benzoic acid. By conjugation of benzoic acid with aminoacetic acid hippuric acid is formed. The amount of hippuric acid excreted depends on the capacity of the liver to synthesize aminoacetic acid. The normal adult is said to excrete from 30 to 35 Gm of hippuric acid in terms of benzoic acid during a period of four hours. Snell and Plunkett¹⁰ found a definite correlation between the amount of hippuric acid excreted and that of bromsulphalein retained in 3 patients who had portal cirrhosis. Fifty patients who present no evidence of disease of the liver or the biliary tract were studied as controls by Yardurman and Rosenthal¹¹. These patients each excreted from 3 to 4 Gm of hippuric acid. The test was found to be of value for patients who suffered from heart failure or impaired renal function, but it was found to be decisive in differentiating hepatic from extrahepatic jaundice, since the patient who has early obstructive jaundice eliminates hippuric acid normally. Lindeboom¹² found the test positive for patients who had primary disease of the liver but found also a diminished output of hippuric acid from those who had obstructive jaundice, heart failure and renal disease. In 30 controls he found the output to be from 2.97 to 4.33 Gm, with an average of 3.73 Gm. He concluded that in a study of disease of the liver the hippuric acid and galactose tolerance tests cannot be relegated to the same category and that there is no exact parallel between the result of Quick's test, the concentration of the serum proteins, and the Takata-Ara reaction.

The urine of those patients to whom this test was applied was treated by the precipitation method of Weichselbaum and Probst¹³.

Bromsulphalein Test—When this test was introduced by Rosenthal and White¹⁴ they recommended the intravenous injection of 2 mg of the dye per kilogram of

7 Liu, S. H., Chu, H. I., Wang, S. H., and Chung, H. L. Nutritional Edema, *Chinese J Physiol* **6** 73-94 (Feb 15) 1932.

8 Thompson, W. H., McQuarrie, I., and Bell, E. T. Edema Associated with Hypogenesis of Serum Protein and Atrophic Changes of the Liver, *J Pediat* **9** 604-619 (Nov) 1936.

9 Quick, A. J. The Synthesis of Hippuric Acid. A New Test of Liver Function, *Am J M Sc* **185** 630-635 (May) 1933.

10 Snell, A. M., and Plunkett, J. E. The Hippuric Acid Test for Hepatic Function, *Am J Digest Dis & Nutrition* **2** 716-721 (Feb) 1936.

11 Yardurman, K., and Rosenthal, P. I. Hippuric Acid Elimination as a Test of Liver Function, *J Lab & Clin Med* **22** 1046-1055 (July) 1937.

12 Lindeboom, G. A. Die Hippursäuresynthese als Leberfunktionsprobe, *Acta med Scandinav* **99** 147-161, 1939.

13 Weichselbaum, T. E., and Probst, J. G. Determination of Hippuric Acid in the Urine, *J Lab & Clin Med* **24** 636-639 (March) 1939.

14 Rosenthal, S. M., and White, E. C. Clinical Application of the Bromsulphalein Test for Hepatic Function, *J A M A* **84** 1112-1114 (April 11) 1925.

body weight O'Leary, Greene and Rowntree¹⁵ considered their results more accurate when they used 5 mg per kilogram of body weight Twenty-two of their patients who were considered to have syphilitic cirrhosis of the liver were found to have dye retention at the end of thirty and sixty minute intervals Retention of the dye, according to the results of Robertson, Swalm and Konzelmann,¹⁶ indicates impairment of liver function as accurately as any other test employed Soffer¹⁷ found results of this test were positive in 55 to 65 per cent of all patients tested who had disease of the liver They were positive in a still higher percentage of patients who had diffuse parenchymal damage, such as results from portal cirrhosis, biliary cirrhosis and prolonged passive congestion The findings of Magath¹⁸ led him to the conclusion that the degree of hepatic damage is more accurately indicated by the bromsulphalein test than by the Takata-Ara or the van den Bergh test or by the albumin-globulin ratio

The test recently has been modified by White and his co-workers¹⁹ They recommend the withdrawal of samples of blood at intervals of two, five and fifteen minutes after injection of 2 mg of the dye per kilogram of body weight Less than 5 per cent of the dye is retained normally at the end of the fifteen minute period In the study reported here the test consisted of injection of 5 mg of dye intravenously and withdrawal of a sample of blood thirty minutes later for determining the amount of dye retained MacDonald²⁰ withdrew blood samples at five minute intervals from normal controls and determined that a dose of 10 mg per kilogram of body weight required sixty minutes for the liver to dispose of the dye, and that with a dose of 6 mg per kilogram thirty-five minutes was necessary When 5 mg was injected, all 25 controls were free of bromsulphalein at the end of twenty-five minutes It is safe to conclude that any dye retention at the end of thirty minutes is abnormal

Cholesterol—Cholesterol esters are said to constitute from 50 to 70 per cent of the normal total cholesterol content of the blood plasma Mancke²¹ reported normal cholesterol values in the plasma of patients who had cirrhosis of the liver, and hypercholesteremia with complete absence of the ester fraction in those who had subacute atrophy Those who had atrophic cirrhosis and were not cholemic were found by Epstein²² to have but little impairment of liver function,

15 O'Leary, P A , Greene, C H , and Rowntree, L G Diseases of Liver Various Types of Syphilis of Liver with Reference to Tests for Hepatic Function, Arch Int Med 44 155-193 (Aug) 1929

16 Robertson, W E , Swalm, W A , and Konzelmann, F W Functional Capacity of the Liver, J A M A 99 2071-2078 (Dec 17) 1932

17 Soffer, L F Present Day Status of Liver Function Tests, Medicine 14 185-254 (May) 1935

18 Magath, T B Takata-Ara Test of Liver Function, Am J Digest Dis & Nutrition 2 713-716 (Feb) 1936

19 White, F W , Datsch, E , and Maddock, S The Comparative Value of Serial Hippuric Acid Excretion, Am J Digest Dis 6 603-610 (Nov) 1939

20 MacDonald, D A Practical and Clinical Test for Liver Reserve, Surg , Gynec , & Obst 69 70-82 (July) 1939

21 Mancke, R , cited by Cantarow, A Cholesterol Metabolism, Internat Clin 1 237-279 (March) 1935

22 Epstein, E Z Cholesterol of Blood Plasma in Hepatic and Biliary Diseases, Arch Int Med 50 203-222 (Aug) 1932

the ability to convert cholesterol into esters was within normal limits Stroebe's²³ findings indicated that the concentration of cholesterol esters in the blood is by no means invariably reduced by severe hepatic disease, but he considered that a continuous decline of these esters is indicative of progressive damage to the liver

In the tests reported here cholesterol was determined by Bloor's method and the cholesterol esters by the method of Weiss

The Patients Studied—According to the procedures mentioned on the first page, a diagnosis of cirrhosis of the liver was made in the cases of 42 patients Thirty-two were men and 10 were women, and their ages varied from the third to

TABLE 1—Data Concerning Forty-Two Patients Studied

	Number of Patients	Percentage
Sex		
Males	33	
Females	9	
Total	42	
Age in decades		
2d to 3d	1	
3d to 4th	9	
4th to 5th	9	
5th to 6th	10	
6th to 7th	9	
7th to 8th	4	
Contributory etiologic factors		
Alcoholism	28	70
Typhoid	3	7
Malaria	2	5
Syphilis	4 positive	10
	Wassermann reactions	
Duration of illness		
Up to 4 weeks	8	
From 1 month to 6 months	15	
From 6 months to 2 years	10	
Over 2 years	3	
Total	36	
Ascites	32	
Jaundice	18	42
Classification of the cases of the forty two patients		
Subacute	17	
Chronic	18	
Undifferentiated	4	
Hemachromatosis	1	
Syphilitic hepar lobatum	2	

the eighth decade Of these patients, the condition in 18 was classified as chronic and in 17 as subacute The conditions in 4 were unclassified, 2 patients had syphilis and hepar lobatum, and 1 had hemochromatosis Practically all stages of cirrhosis were represented Symptoms had been of short duration, 23 of 36 patients having been sick for six months or less Alcoholism was considered to be a contributing factor in a minimum of 28 patients, the blood of 4 gave a positive Wassermann reaction, and 3 had had typhoid fever Thirty-two had ascites, 8 had been jaundiced, and 10 were jaundiced at the time of study Some details of these conditions are contained in table 1 Details of the results obtained in the study are recorded in table 2, and a summary of the results is found in table 3

23 Stroebe, F Zur Cholesterinamie bei Lebercirrhose und hepatocellulärem Ikterus, Klin Wchnschr 11 636-639 (April 9) 1932

TABLE 2—Detailed Results of Examination of 42 Patients Studied

Pa- tient	Sex	Age	Ascites	Jaun- dice	Van Den Berg's Reaction	Brom- sulph phen- ol Reten- tion	Hippuric Acid	Non protein Nitro- gen	Serum Protein	Serum Albu- min	Serum Glob- ulin	Albu- min/ Glob- ulin	Choles- terol and Esters	Diagnosis	
														Peritoneoscopic Examination	Biopsy
1	M		0		13 units		2.5 Gm	40						Atrophic cirrhosis, hydrops of gallblad- der, splenomegaly	Probably hyperplastic nodule in cirrhotic liver
2	M	60	2,500 cc., 12 wks			50%								Atrophic cirrhosis	Chronic cirrhosis, Laennec's type
3	M	39	3,000 cc		1 units	30%	4.3 Gm			3.0 2.8	2.0 1.9	1.5 1.47		Cirrhosis	Hyperplastic nodule possible cirrhosis
4	M	29	0	0		Less than 5%	4.97 Gm						Fibrosis of liver capsule		Chronic cirrhosis, Laennec's type
5	F	46	2,000 cc	+	21 units 23 mg Takata Ara + + + + +	1%	3.3 Gm			2.0	2.7	0.71		Atrophic cirrhosis	Histologic findings normal, biopsy unsatisfactory
6	M	60	10,000 cc	0		30%	3.91 Gm							Advanced cirrhosis	Chronic cirrhosis, Laennec's type
7	M			0	5 units	100%	1.18 Gm	28		3.8	1.1	1.22		Perihepatitis asso- ciated with fibrosis of liver capsule	Chronic cirrhosis, chronic perihepatitis
8	F	64	10,000 cc	+	77 units 6.7 mg 111 units 17 mg Takata Ara +			26		2.3	1.1	0.66	192 (25%)	Atrophic cirrhosis, far advanced	Chronic cirrhosis with rupture of esophageal varices, bronchopneu- monia, autopsy
9	M		+	0	7 units	60%	2.13 Gm		6.4 ml.				192 (38%) 208 (21%)	Cirrhosis	Chronic cirrhosis, Laennec's type
10	M	39	+	0	9 units Takata Ara +	25%	2.9 Gm	21		2.7	2.9	0.90	227 (31%)	Cirrhosis and splenomegaly	Chronic cirrhosis, Laennec's type

11	M	57	+	0	20%	2.5 Gm	7.1 mL	1.9	2.9	0.6	20% (60%)	Cirrhosis	Advanced cirrhosis, nodular liver	Chronic cirrhosis, Laennec's type
12	M	54	15,000 cc		75%			2.1	1	0.6	161	Atrophic cirrhosis, prothrombin, 75% nodular liver, hobnailed		Chronic cirrhosis, Laennec's type, pulmonary tuberculosis, at autopsy
13	M	65	20,000 cc, 3 mo	0	25%			1.9	2.9	0.6	20% (60%)	Cirrhosis		Chronic alcoholic cirrhosis
14	F	70	6,000 cc	++	57 units 68 units	1.5 Gm		2.1	1	0.6	161	Atrophic cirrhosis, prothrombin, 75% nodular liver, hobnailed		Chronic cirrhosis
15	M	48	30,000 cc, 19 taps	0	50%	1.7 Gm	6.6 mL				136 Total lipids 580	Cirrhosis, fat content of ascitic fluid, 2 Gm in each 100 cc		Chronic cirrhosis
16	M	53	7,000 cc, 5 mo	0	70%	1.86 Gm	5.3 mL	2.0	0.3	0.83	208 161	Atrophic cirrhosis		Laennec's cirrhosis, far advanced
17	M	48	8,000 cc, 5 mo, 8 taps		40%	2.2 Gm	27	2.0	2.3	0.87	136	Chronic cirrhosis, hobnailed liver		No biopsy
18	M	38	4,000 cc			4.76 Gm	5.7 mg	2.4	1.9	1.26	131 (87%) Lipids 512	Cirrhosis, galactose tolerance, 1.3 Gm		Hemachromatosis
19	M		3,000 cc		12.5 units	2.8 Gm	6.5 mg	2.2	1.1	0.70	161	Subacute cirrhosis galactose tolerance, 0.6 Gm, dextrose tolerance, 1 hr 78, 2 hr 100, 3 hr 91, 4 hr 101		Late subacute cirrhosis, no autopsy at death of patient
20	F	56	0	++ 7 mo ago	9.5 units 0.9 mg			2.6	1.2	0.61		Subacute hepatitis, early cirrhosis		Subacute hepatitis
21	M	70			50%							Cirrhosis		Late subacute alcoholic cirrhosis
22	M	39		0	7 units	3.61 Gm		3.5	3.1	1.12		Subacute cirrhosis		Subacute alcoholic cirrhosis
23	M	62	4,000 cc, 1 mo	++	16 units	2.61 Gm		2.2	1.5	0.78	1.2	Cirrhosis with splenomegaly		Late subacute alcoholic cirrhosis
24	M	67	1,000 cc	0	6 units	1.61 Gm	29	2.8	2.6	1.07	192 (60%)	Anatomic diagnosis, weight of liver, 1,000 Gm weight of spleen, 870 Gm portal cirrhosis, islets, benign nephrosclerosis, rheumatic mitral stenosis		Subacute chronic cirrhosis

TABLE 2—Detailed Results of Examination of 42 Patients Studied—Continued

Pa tient	Sex	Age	Ascites	Jaun dice	Van Den Bergh Reaction and Icteric Index	Brom sulph alein Reten tion	Hippuric Acid	Non protein		Serum Albu min	Serum Glob ulin	Albu min/ Glob ulin	Choles terol and Esters	Diagnosis	
								Nitro gen	Serum Protein					Peritoneoscopic Examination	Biopsy
25	M	32	Small amount of fluid	0									200 117 (55%) Lipids 903	Subacute Laennec's cirrhosis, dextrose tolerance 92 at 7 15, 104 at 8 15, 81 at 9 15 and 85 at 10 15, galac tose, trace, liver enlarged	Subacute alcoholic cirrhosis (fatty)
26	M	36	20,000 cc	0	13.3 units 10.8 units	50%	1.12 Gm		6.6 mg	2.2	3.8	0.57	204	Subacute cirrhosis, extremely enlarged liver	Subacute alcoholic cirrhosis
27	M	55		++	57 units 5.3 mg 19 units 1.5 mg 12 units 0.07 mg	Less than 15%	4.1 Gm 2.79 Gm						370 200 (54%)	Subacute cirrhosis, large granular liver	Subacute alcoholic cirrhosis, operation for obstruction of the common duct at ampulla, probable neoplasm, benign or malignant
28	M	41	+++				3.55 Gm							Late subacute alco holic cirrhosis	Late subacute alco holic cirrhosis
29	M	42	1,200 cc	0	2.9 mg 38 units 9 units		1.5 Gm			3.2	2.9	1.09	125 48 (39%) 178 78 (43%) B lip 518	Subacute alcoholic cirrhosis, galactose tolerance, 0.04 Gm, phosphatase, 6.8 units, phosphorus, 2.4	Subacute alcoholic cirrhosis
30	M		+++	++	7.2 mg 67 units 6.3 mg 62 units 2.2 mg 26 units 22 mg 1.7 mg 15.7 units		4.60 Gm			2.9	2.9	1.06	Lipids 716 mg 219 135 (62%) Lipids 978 238 107 (45%) Lipids 800	Subacute cirrhosis	Subacute alcoholic cirrhosis, fibrosis ++++, fat ++++ necrosis of liver cells ++ , galactose tol erance, 0.4 Gm
31	M	33	3,500 cc	++						3.5	4.2	0.83	278	Subacute cirrhosis with ascites	Subacute alcoholic cirrhosis

32	M	50	4,000 cc, 13 yr	0	8 units	75%	2.5	2.9	0.80	Cirrhosis	Subacute alcoholic cirrhosis, death from ascites, esophageal varices with hemorrhage, and intestinal obstruction
33	F	49	7,000 cc	0	33 units 2.2 mg 28.5 units Takata Arn + 5.5 mg 51 units 20 units		1.1 1.6 1.5 1.8 1.1	3.8 3.8 3.8 3.3 2.9	0.36 0.42 0.59 0.51 0.48	Subacute cirrhosis, blood sugar, 299 mg in each 100 cc, amino acid nitrogen, 6.2 mg	Late subacute cirrhosis, hema chromatosis
34	M	47	5,500 cc	0	5.7 units	37%	5.8 mg		200 (21%)	Subacute cirrhosis, liver moderately enlarged	Late subacute cirrhosis
35	M	46	0	++	53.2 units 40 units 13 units		8.6 mg		178	Acute hepatitis, liver slightly enlarged, galactose, trace	Laennec's cirrhosis, subacute hepatitis, left hepatic well
36	M	73	0	++	40 units		1.36 Gm	2.9	0.9	Subacute cirrhosis, granular liver	Subacute cirrhosis, autopsy
37	F	46	1,900 cc, 9 mo	0		0%	6.3 mg	3.1 4.0 2.9 2.7	1.0 1.33 2.2 0.93	Cirrhotic changes on the basis of long standing chronic passive congestion	Chronic cirrhosis, type unknown, final impression, coronary disease with posterior infarction, autopsy
38	F	52			7 units	20%		2.6	1.13	Cirrhosis	No biopsy
39	M	57	4,500 cc	0	5 units	50%		2.3		Nodular cirrhosis, hepatic lobatum	Gumma of liver
40	F	69	10,000 cc	+	5.5 units	55%	5.7 mg	3.1	1.19	Cirrhosis, probably syphilitic	Cirrhosis, syphilitic, hepatic lobatum, death from condition of liver, autopsy
41	F	67			4.4 units	Less than 10%		1.2	0.57	No peritoneoscopic examination	Hypertensive heart disease, blood pressure 225/130, duodenal ulcer, gastric hemorrhage, roentgen studies
42	M	56	6,000 cc		5 units	40%	10.5 mg		111	Atrophic cirrhosis, nodular liver	Late subacute or chronic cirrhosis, hypertensive heart disease and chronic cirrhosis with ascites at autopsy

RESULTS

A summary of the results of liver function tests done is found in table 3. From a study of this and of the details in table 2, it is seen that the most reliable results are those obtained by the bromsulphalein test and by determination of the serum proteins and the albumin-globulin ratio.

If one makes the liberal allowance of 10 per cent retention of bromsulphalein thirty minutes after the intravenous injection of 5 mg per kilogram of body weight as being within normal limit, it is seen that in 22, or 78 per cent, of the 28 patients tested the results indicate definitely impaired liver function. None of these patients was jaundiced when the test was made.

TABLE 3—Results of Tests

Number of Patients	Test	Result
28	Bromsulphalein	Positive in 22 patients Negative in 6 patients
32	Hippuric acid *	Positive in 18 patients Negative in 14 patients
21	Albumin globulin	Positive in 15 patients Negative in 6 patients
16	Cholesterol and esters	Positive in 9 patients Negative in 7 patients
6	Takata Aza	Positive in 4 patients Negative in 2 patients
10	Jaundice at time of interview	

* The result of the hippuric acid test was negative in 4 patients who gave positive reactions to the bromsulphalein tests and positive in 1 instance in which a negative reaction to the bromsulphalein test was obtained.

The total serum proteins and the albumin-globulin ratio were determined in 21 patients. In 15 of these, 72 per cent, the total proteins were definitely below normal and the ratio of albumin to globulin was reversed.

The hippuric acid test was done on 32 patients, and in 18, or 56 per cent, of these the results indicated impaired liver function. Blood cholesterol and cholesterol esters were determined in 16 patients, and in 9, or 56 per cent, of these the results indicated impaired liver function. It should be mentioned that the methods used in the last determinations are tedious and subject to considerable error.

From the standpoint of prognosis, the importance of failure to excrete bromsulphalein, reduction in serum proteins and reversal of the albumin-globulin ratio in the same patient should be emphasized. None of the patients in this group who were found to have these conditions lived longer than six months. It may be said that these findings indicate a high degree of damage to the endothelial system of the liver and to the ability of the liver to synthesize proteins and that under these circumstances, nothing more than temporary improvement of the patient's health can be expected.

COMMENT

Causes of Impaired Liver Function—It becomes increasingly apparent that liver function bears a direct relation to the state of nutrition of the organ. A deficiency of glycogen renders the liver especially susceptible to injury. According to Moon²⁴ the following agents are capable of producing cirrhosis of the liver: bacterial infections (toxins?), manganese chloride plus phenylhydrazine, carbon tetrachloride, tars and phosphorus plus alcohol. An abnormal degree of fatty change is found in the livers of malnourished, emaciated persons. Increased amounts of fat in the hepatic cells of starving animals were described by Dible and Libman²⁵. In rats whose fat reserve was meager the increased fat in the liver was only relative, but when the fat stores were sufficient to permit mobilization, an absolute increase was found in the liver. The condition is found in the livers of those who suffer from diseases of the intestinal tract that produce diarrhea. Best and Campbell²⁶ stated that fatty livers may be produced in experimental animals by fasting, by feeding diets rich in fats, by feeding cholesterol and by phosphorus poisoning. Injection of pituitary substance has been found to be followed by increased amounts of fat in the livers of fasting and fed rats. Friedenwald²⁷ found that after prolonged administration of alcohol to rabbits their livers contained abnormal amounts of fat. This change was reversible, and the fat would disappear soon after the administration of alcohol was stopped. The presence of fat in the liver, with few exceptions, was considered abnormal by Connor²⁸. He stated that under certain circumstances fat may accumulate in the human liver within forty-eight hours and disappear rapidly after the administration of dextrose. It is also maintained that at autopsy as much as 60 per cent of the livers of chronic alcoholic addicts may consist of fat, and that if this condition persists for a sufficient length of time the sinusoids collapse, portal circulation becomes blocked and parenchymatous anoxemia follows. It has been demonstrated by Bollman²⁹ that fatty livers develop in fasting dogs and other experimental animals living

24 Moon, V. H. Experimental Cirrhosis in Relation to Human Cirrhosis, *Arch. Path.* **18** 381-424 (Sept.) 1934.

25 Dible, J. H., and Libman, J. Further Observations on Fat Mobilization in Starvation, *J. Path. & Bact.* **38** 269-284 (May) 1934.

26 Best, C. H., and Campbell, J. Anterior Pituitary Extracts and Liver Fat, *J. Physiol.* **86** 190-203 (Feb. 8) 1936.

27 Friedenwald, J. The Pathologic Effects of Alcohol on Rabbits, *J. A. M. A.* **45** 780-784 (Sept. 9) 1905.

28 Connor, C. L. Fatty Infiltration of the Liver and Development of Cirrhosis in Diabetes and Chronic Alcoholism, *Am. J. Path.* **14** 347-364 (May) 1938.

29 Bollman, J. L. Some Experimental Observations Pertinent to Treatment of Hepatic Disease, *Ann. Int. Med.* **12** 2-5 (July) 1938.

on a diet high in fat and that administration of alcohol intensifies this change. He found also that if dogs were given a well balanced diet and large amounts of alcohol the liver remained normal.

The dietary deficiency usually associated with alcoholism is in itself detrimental to liver metabolism. Lipschitz³⁰ and his co-workers found that vitamin B₁ deficiency was followed by serious impairment of the pyruvic acid metabolism in the liver and by deranged carbohydrate metabolism in the entire organism. By a study of the food habits of 131 alcoholic addicts, Romano³¹ found that 58 per cent of them had some degree of neuritis and that 79 per cent took inadequate amounts of food.

Cirrhosis of the liver may be found as frequently in some countries where alcohol is used but little as in others where its use is habitual, but a common predisposing factor is present in each instance, namely, failure of alimentary absorption. Yenikonshian³² stated the belief that malaria and dysentery, or a combination of these, are important factors in the production of cirrhosis of nonalcoholic origin among the natives of Syria and Lebanon. Infestation by intestinal parasites is prevalent among these peoples, and the average age of those who acquire cirrhosis of the liver is much lower than it is in this country. According to a report by Rolleston and McNee³³ cirrhosis of the liver is much more frequent among the natives of India than it is among the white people. Records of 535 autopsies done on natives of Vizagapatam revealed that 93 per cent had cirrhosis of the liver. Twenty-five patients were found to have portal cirrhosis. Tirumurti³⁴ and his co-worker emphasized the fact that the people of this locale do not drink alcohol. It was affirmed by Bloomfield³⁵ that cirrhosis of the liver may progress to a far advanced stage before it causes symptoms or produces changes which induce the patient to seek medical care and by the same token may cause the clinician to fail to make a correct diagnosis. In most instances a review of the history gives no indication as to the time of onset of the

30 Lipschitz, M. A., Potter, V. R., and Elvehjem, C. A. Metabolism of Pyruvic Acid in Vitamin B₁ Deficiency and Inanition, *J Biol Chem* **123** 267-281 (March) 1938

31 Romano, J. Deficiency Syndromes Associated with Chronic Alcoholism, *Am J M Sc* **194** 645-651 (Nov.) 1937

32 Yenikonshian, H. A. Non-Alcoholic Cirrhosis of the Liver in Lebanon and Syria, *J A M A* **103** 660-661 (Sept. 1) 1934

33 Rolleston, H. D., and McNee, J. W. Diseases of Liver, Gall Bladder, and Bile Ducts, ed. 3, New York, The Macmillan Company, 1929

34 Tirumurti, T. S., and Radhakrishna Rao, M. V. Incidence of Portal Cirrhosis of the Liver in Vizagapatam, *Indian M Gaz* **69** 74-76 (Feb.) 1934

35 Bloomfield, A. L. The Natural History of Chronic Hepatitis, *Am J M Sc* **195** 429-444 (April) 1938

disease Also the prognosis is uncertain, because of a lack of knowledge concerning the complex alterations of metabolism that result from disease of the liver

Causes of Death of Patients Who Have Cirrhosis of the Liver—In an analysis of the clinical and autopsy records of 217 patients in the Los Angeles County Hospital who were found to have alcoholic cirrhosis of the liver, Evans and Gray³⁶ found the causes of death to be as follows

<i>Causes of Death</i>		
	No	Per Cent
Pneumonia		
Lobular	73	} 37 0
Lobar	8	
Gastrointestinal hemorrhage	43	20 0
Insufficiency of the liver	26	12 0
Peritonitis	10	4 6
Miscellaneous	57	21 0

The present study includes an analysis of the autopsy records of 102 patients whose conditions were similar to those found in the aforementioned group, but which were classified as being associated with subacute or chronic cirrhosis The causes of death in this group were tabulated as follows

	<i>Causes of Death</i>			
	Subacute		Chronic	
	No	Percentage	No	Percentage
Pneumonia	16	33	15	28
Gastrointestinal hemorrhage	13	27	17	31
Insufficiency of the liver	10	20	12	22
Miscellaneous	9	20	10	19

From these figures it appears that the prognosis in patients who have cirrhosis of the liver does not correspond to the histologic picture described by the pathologist Regardless of the probable criticism that the division of these pathologic pictures into two groups is only an approximation, the fact remains that these patients die of identical causes, and in about the same ratios, whether they have large, smooth or small, fibrotic, hobnailed livers The classification was made according to certain arbitrary rules If the liver weighed more than 2,000 Gm, contained an extensive amount of fat or showed evidence of necrosis, the cirrhosis was classified as subacute If the liver was smaller, had irregular, scarred surfaces and presented unusual resistance to cutting, the cirrhosis was designated as chronic

Hall and Morgan³⁷ described the subacute cirrhotic liver as being large, as weighing from 2,000 to 5,000 Gm, as having a smooth or finely

36 Evans, N, and Gray, P A Laennec's Cirrhosis Report of Two Hundred and Seventeen Cases, J A M A **110** 1159-1161 (April 9) 1938

37 Hall, E M, and Morgan, W A Progressive Alcoholic Cirrhosis, Arch Path **27** 672-690 (April) 1939

granular surface and as being usually fatty. Fibrosis is not as extensive and the tissue is more cellular than that of the liver which presents chronic atrophic cirrhosis. Necrosis of the hepatic cells is prevalent, this is conspicuously absent in the chronic form.

When the ages of these groups of patients are studied in graphs a conspicuous difference between the two conditions is seen, the peaks

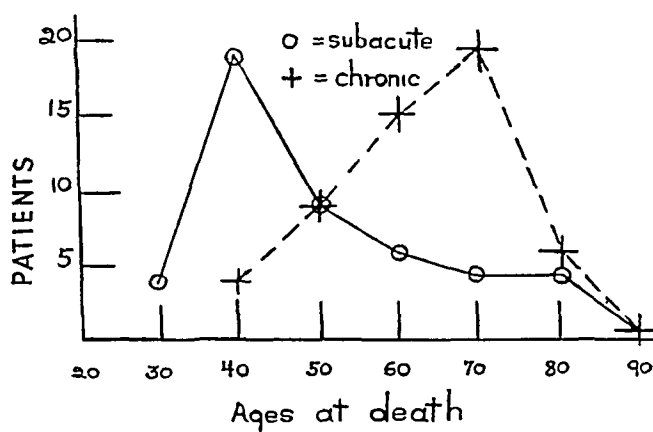


Fig 1—Comparison of the ages at death of patients with subacute cirrhosis of the liver and those of patients with chronic cirrhosis of the liver

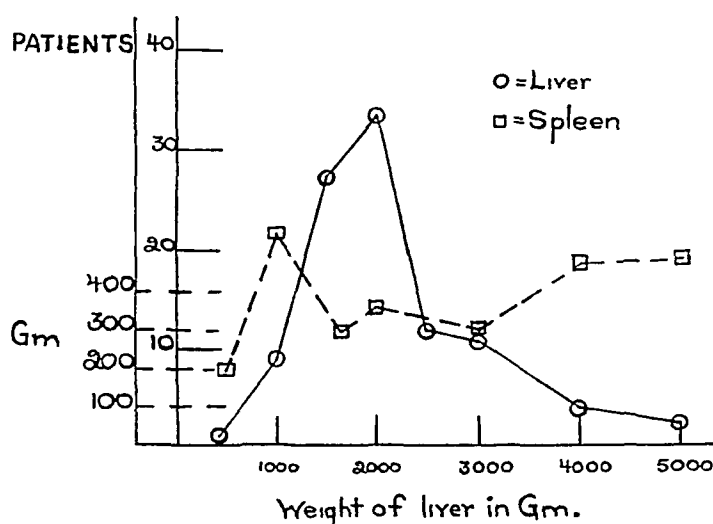


Fig 2—Comparison of the weight of the liver and that of the spleen in patients with cirrhosis of the liver

indicating the age of greatest incidence of the two conditions are two decades apart (fig 1). This is considered to be related to the pathogenesis of the separate conditions. There appeared to be no definite relationship between the weights of the liver and of the spleen (fig 2). In chronic cirrhosis of the liver, parenchyma is replaced by fibrous tissue, and even though there is extensive regeneration and hypertrophy

of the cells of the liver, the size of the organ decreases as a result of contraction of fibrous tissue. It should be emphasized again that the liver function cannot be judged by the degree of these changes, as indicated by the gross or even the microscopic appearance of the tissue.

Studies of Liver Function in Patients with Acute Alcoholism—After a study of liver function as indicated by a variety of tests in patients in whom biopsy of the liver proved varying degrees of cirrhosis of liver, it was decided to apply some of these same tests to a group of patients who were recovering from severe alcoholic intoxication. The 17 men selected for this study were tested within twenty-four hours after they had been detained because of intoxication. Only those who had been

TABLE 4—*Results of Liver Function Tests in Patients with Acute Alcoholism*

Patient	Age	Retention of Brom sulphalein	Serum Protein	Serum Albumin	Serum Globulin	Cholesterol	
						Total	Esters
1	53	0					
2	53	0					
3	50	20%					
4	42	5%					
5	58	Less than 10%	6.7	3.5	2.5		
6	64	Less than 10%		5.3	2.6		
7	52	0	5.9	3.8	1.9		
8	52	20%	6.4	3.5	2.0		
9	31	0	6.2	4.1	2.6		
10	56	Less than 10%	6.5	3.9	2.3		
11	52	0		2.9	2.4	208	141 (67%)
12	62	10%		3.2	2.3	178	91 (51%)
13	40	0		3.9	2.6	166	61 (37%)
14	62	0		3.8	1.8	208	111 (47%)
15	51	20%		2.6	2.4	172	88 (51%)
16	49	0		3.8	2.8	227	111 (51%)
17	45	0		3.5	2.6	156	72 (46%)

drinking for two or more weeks and who had taken but small amounts of food were studied. Each patient complained of nausea and anorexia and had a pronounced tremor, but none had an enlarged liver, jaundice or evidence of peripheral neuritis.

The bromsulphalein test was done on each of the 17. Serum albumin and globulin were determined in 13, cholesterol and cholesterol esters in 7. Four of the 17 patients retained 10 per cent or more of the bromsulphalein for more than thirty minutes, which retention indicated impaired liver function. Serum albumin and globulin were within normal limits, and with one exception cholesterol esters were normal. Patient 13 did not retain an abnormal amount of dye, but his cholesterol esters were 37 per cent, 40 per cent was considered the lower limit of normal. There was no opportunity to do follow-up studies on these patients, so it can only be said that in the stage in which they were studied their ability to excrete bromsulphalein was impaired.

The results of the tests are seen in table 4.

An effort is being made to do liver function tests on those patients in whom the tests indicated a damaged condition of the liver when they are between their drinking bouts and to continue studies on them as long as possible

SUMMARY

The liver function tests used in a study of 42 patients who had proved cirrhosis of the liver and 17 who suffered from acute alcoholism are discussed

Some of the causes of impaired liver function are discussed briefly

The diagnosis made as a result of the appearance of the liver as seen through the peritoneoscope and that made by the pathologist who examined the specimen taken for biopsy paralleled each other with surprising accuracy

The established variations in degree of organic change in the livers of these patients in conjunction with the results of liver function tests indicate that the use of these tests is justified from the standpoint of diagnosis, plan of management and prognosis

Results of the function tests used, considered with the histologic diagnosis made on the respective patients, indicate that these tests may be arranged in the following order, according to their value in clinical studies bromsulphalein test, determination of the total serum proteins and the serum albumin-globulin ratio, hippuric acid test and determination of the serum cholesterol and the cholesterol esters

The results of tests on patients with acute alcoholism indicate that early and perhaps temporary impairment of liver function may be detected by the bromsulphalein test Additional studies on this type of patient are under way

1930 Wilshire Boulevard

FATAL BRONCHIAL ASTHMA

REPORT OF SEVEN CASES

BRANCH CRAIGE JR, M D

NEW HAVEN, CONN

Death rarely comes to patients in status asthmaticus Thieme and Sheldon,¹ summarizing the literature prior to 1937, counted only 43 cases with autopsy reports in which the patient died in an asthmatic paroxysm They added 7 such cases and since then additional cases have been reported by Fowler² and by Lamson and Butt³

Of 56,000 admissions to the medical service of the Peter Bent Brigham Hospital, 1,378 represented those of 992 patients who had had either a primary or a secondary clinical diagnosis of bronchial asthma, of this number 49 died Autopsies were performed on 23 of these 49 patients In 7 of these 23 patients the clinical picture was that of status asthmaticus, the autopsy observations were consistent with bronchial asthma and no extrapulmonary cause of death was present

The 7 cases are herewith reported

CLINICAL FINDINGS

The patients were all women between the ages of 24 and 67, with a mean age of 45 In 6 cases the primary clinical diagnosis was bronchial asthma The duration of the disease was six months to fourteen years, and its onset was in most instances subsequent to an infection of the respiratory tract There was no uniformity in regard to the time of year in which the fatal attack occurred, and its duration was also variable, ranging from two days to several weeks The cause of the asthma in these cases was obscure and the results of cutaneous tests in 6 instances were inconclusive

Examination in every case revealed great respiratory distress with exaggerated difficulty in expiration Appreciable cyanosis was observed in 4 cases In only 4 cases of the group was the anteroposterior diameter of the chest increased In 5 cases the heart was entirely normal as far

From the Department of Pathology, the Peter Bent Brigham Hospital, Boston

1 Thieme, E T, and Sheldon, J M Correlation of Clinical and Pathologic Findings in Bronchial Asthma, *J Allergy* **9** 246-269 (March) 1938

2 Fowler, K Necropsy Studies on Two Patients Dying in Asthma, *Pennsylvania M J* **40** 720-724 (June) 1937

3 Lamson, R W, and Butt, E M Fatal "Asthma" Clinical and Pathologic Consideration of One Hundred and Eighty-Seven Cases, *J A M A* **108** 1843-1850 (May 29) 1937

TABLE 1—Results of Clinical Study of Seven Patients Who Died of Asthma

Name	A D	L McD	B B	I B	R M	E K	G C
Age	45	53	40	45	49	23	67
Occupation	None	Housewife	Housewife	Secretary	Housewife	None	None
Sex	Female	Female	Female	Female	Female	Female	Female
Complaint	Asthma	Dyspnea, coma	Asthma	Asthma	Asthma	Dyspnea, asthma	Asthma
Allergy, family history	None	None	None	None	None	None	Family history hives
Allergy, past history	None	None	None	None	None	None	None
Duration of asthma	6 months	14 years	2 years	7 years	9 years	7 years	7 years
Condition preceding onset	"Bronchitis"	"Cold"	"Exposure"	"Influenza"	Pneumonia	"Cold"	
Seasonal or other incidence	None	Bedtime	Catamenial	None	Nocturnal	None	Fall
Cutaneous tests	None	Negative	Positive to wheat, egg and beef	Negative	Positive to green peas, pollen	Negative	Negative
Duration of terminal illness	? weeks	6 weeks	1 month	2 weeks	2 months	3 weeks	3 weeks
Date of death	Feb 12	Feb 21	June 9	Oct 21	Sept 10	July 25	Oct 23
Findings on physical examination							
Cyanosis	None	Appreciable	Appreciable	Appreciable	Asthenic,	None	Appreciable
Shape of chest	Barrel	Barrel	Normal	Barrel	pigeon breast	Long, narrow	Slightly thickened
Heart	Enlarged to left	Normal	Normal	Normal	Normal	Normal	Normal
Lungs Percussion note	Resonant, ape\ dull	Hyperresonant	Resonant	Hyperresonant	Hyperresonant	Hyperresonant	Hyperresonant
Rales	Musical	Occasional dry rale	Squeaking, musical	Squeaking, groaning	E\phratory, musical	Wheezing, groaning, musical	Sibilant, sonorous
Signs simulating failure of right side of heart	Edema		L edema			Distended veins of neck	Palpable liver?, edema, distended veins of neck
Temperature, degrees F	98 to 102	98 to 101	98.4 to 99	99 to 99.6	98 to 99	98 to 106	100.2
Pulse rate	100 to 148	92 to 130	96 to 100	105 to 135	80 to 136	88 to 140	70 to 140*
Respiratory rate	10 to 35	20 to 30	24 to 32	25 to 32	15 to 30	27 to 48	24
Blood pressure	115/80	138/88	132/92	Expiratory 160/100, Inspiratory 145/90	126/94	130/90	130/60
Electrocardiogram	Normal curves				Normal curves	Abnormal form of ventricular complex	
Laboratory data							
Red blood cells	4,000,000	5,100,000	4,100,000	5,200,000	5,300,000	5,500,000	
Hemoglobin (per cent)	70	80	70	96	100	100	
White blood cells	11,200	8,900	10,000, 3,800	15,600	7,300	17,400	
Polymorphonuclear leukocytes (per cent)	48	70	72	75	~2	88	
Eosinophils (per cent)	11	1	4	0	3	0	
Outstanding terminal signs	Dyspnea weakness	Cyanosis, dyspnea	Cyanosis res piratory failure	Dyspnea	Dyspnea	Dyspnea, exhaustion hyperpyrexia	Slow respiration exhaustion
Respiratory failure preceding car- diac failure		Yes	Yes	No			

* Cardiac rate shifted between 72 and 110 at fifteen second intervals

as physical examination was concerned, in the other 2 cases the findings were enlargement, in 1, and a cardiac rate shifting between 72 and 140, in the other. The pulse rate was nearly always elevated, rarely ranging as low as 88 and usually lying between 100 and 140. In some instances there were signs simulating right-sided heart failure, such as a questionably enlarged liver, in 1 case, distention of the veins of the neck, in 2 cases, and dependent edema, in 3 cases.

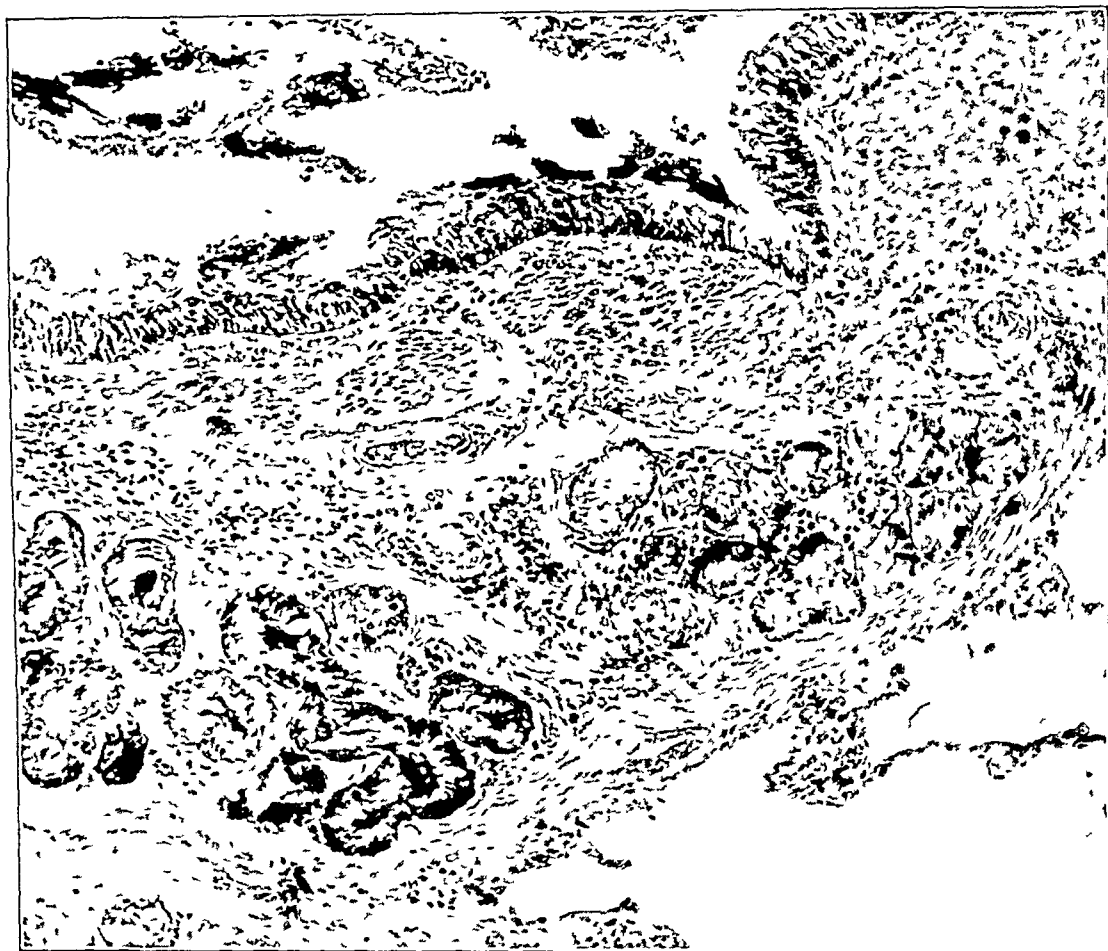


Fig 1—The wall of a bronchus ($\times 100$) in a patient who died of bronchial asthma. Note the hypertrophied musculature, the bronchial glands distended with thick mucus, the hyaline basement membrane and the thickening of the submucous layer. Many of the cells are eosinophils.

The lungs were hyperresonant with sibilant and sonorous rales, wheezes and groans, but no crackling rales. The expiratory phase was prolonged, and in 1 case it was noted that the breath sounds were uniformly diminished. There was, however, no uniformity in the respiratory rate. The blood pressure was normal in all instances, and fever was observed in 4 cases. The blood showed a high eosinophil count in only 2 cases, 11 and 4 per cent, respectively. In the other 4 in which blood counts were recorded the eosinophils averaged 2 per cent.

In the terminal stages the patients failed to get adequate relief from epinephrine, became more dyspneic, and sometimes more cyanotic, and died. In 2 instances it was noted that the heart continued to beat for some time after respirations ceased.

The pertinent clinical findings are summarized in table 1.

POSTMORTEM OBSERVATIONS

At autopsy in every case the voluminous, feathery lungs completely filled the pleural cavity and in several instances actually bulged out over



Fig 2—Curschmann's spiral within the lumen of a bronchus ($\times 50$) in a patient who died of bronchial asthma.

the mediastinum on removal of the breast plate. The weight of the lungs averaged 300 Gm each in the 4 instances in which it was determined. The cut surface showed, in all instances but 1, a large amount of thick, viscid, tenacious, elastic, mucoid material in the middle-sized (3 to 6 mm) bronchi.

Microscopic sections showed emphysema in all cases. The severest lesions were observed in the middle-sized bronchi (fig 1). In 6 cases

thick plugs were found in these bronchi. The plugs all contained eosinophils, and in 4 cases Cusschmann's spirals were recognized (fig 2). In 4 cases the mucus plugs in the bronchial lumen contained Charcot-Leyden crystals (fig 3). The bronchial mucosa showed metaplasia in only 1 instance, but in 6 instances it was thrown up into folds, and frequently small sacculations of the mucosa could be seen. The mucosa and submucosa were infiltrated with lymphocytes and varying numbers of eosinophils, but the mucous glands, cartilage and musculature usually

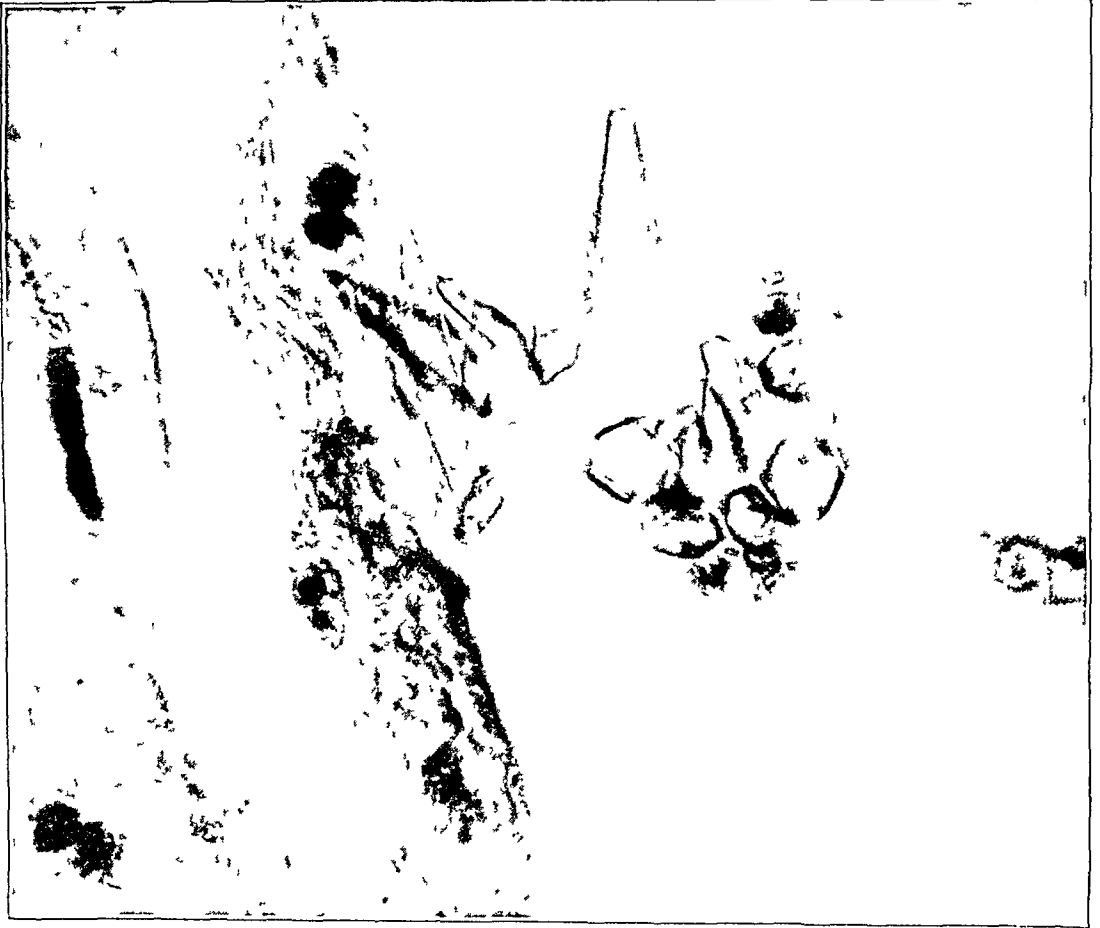


Fig 3—Charcot-Leyden crystals in the mucus within the bronchial lumen ($\times 1,500$) in a patient who died of bronchial asthma. Several appear in cross section, showing six sides. Others appear in profile, giving the appearance of a double pyramid.

escaped infiltration with such cells. In all cases the submucosal layer was widened and the basement membrane was thick and hyaline. Hypertrophy of the bronchial musculature, present in every case, varied from bronchus to bronchus, being extreme in some bronchi and absent in others. Inspissated mucus distending the bronchial glands, with pressure atrophy of the acinic cells, was frequently seen; it occurred in the 5 cases in which glands were present for examination. The amount of such

TABLE 2—*Postmortem Observations*

Name	A D	L McD	B B	I B	R M	E K	G O
Macroscopic Examination Thorax after opening	Lungs bulging from beds	Lungs volu- minous, bulging, part of me- diastinum	Lungs meeting in midline, obscuring mediastinum	Lungs meeting anterior to pericardium	Lungs com- pletely filling pleural spaces	Lungs bulging	Lungs bulging over mediastinum
Pleural cavities	Apical adhesions	Apical adhesions	Apical and basal adhesions	Apical adhe- sions	Normal	Adhesions throughout	Normal
Lungs Weight (Gm)	240, 220	240, 220	230, 240			340, 320	420, 290
Gross appearance	Grayish yellow, rounded, emphy- sematous	Pallid, voluminous	Voluminous	Pallid, emphy- sematous	Pale, distended	Doughy, re- taining shape	Voluminous, doughy, one area of consolidation, several areas of atelectasis
Bronchi	Tenacious, mucinous material	Minute amount of mucoid exudate	Almost all plugged with tenacious, glairy mucus	Almost all plugged with gelatinous, tenacious mucus	Completely plugged with tenacious, thick, cloudy, ad- herent mucus	Mucus plugs, frothy, purulent mucus	Plugs of thick, white, elastic, tenacious, mucus
Apexes	Normal	Scarred	Scarred	Indurated	Normal	Normal	Scarred
Heart							
Weight (Gm)	365	320	200	310	300	200	260
Chambers	Slight dilata- tion of right auricle	Normal	Normal	Slight promi- nence of right auricle and right ventricle	Normal	Normal	Normal
Thickness of musculature, left and right ventricles (mm)	14, 5	14, 4	13, 3	15, 3	8, 1	9, 3	14, 5
Coronary arteries	Normal	Slight sclerosis	Normal	Normal	Normal	Normal	Normal
Valves	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Liver	Slight congestion †	Congestion	Congestion	Normal	Not ex- amined	Congestion	Congestion

Ankles	Normal	Normal	Edema	Normal	Normal	Edema
Skin						Cyanosis
Other organs	No significant lesions	Chronic pancreatitis	Hyperplasia of thyroid, mild ptosis of kidney	No significant lesions	Examination limited to chest	No significant lesions
Microscopic Examination						
Lungs						
Bronchi						
Lumen	Mucus plugs, O L* crystals, O† spirals, eosinophils	Almost free of mucus, few eosinophils	Mucus plugs, O spirals, eosinophils	Mucus plugs, O L crystals, O spirals, eosinophils	Mucus plugs, eosinophils	Mucus plugs, O L crystals, O spirals, eosinophils
Mucosa	Thickened, infolded, sacculated, no metaplasia	Thickened, infolded, sacculated, no metaplasia	Thickened, infolded, sacculated, no metaplasia	No thickening, infolding, or metaplasia, sacculated	Slightly thickened, infolded, sacculated, no metaplasia	Thickened, infolded, sacculated, no metaplasia
Basement membrane	Wide, hyaline	Wide, hyaline	Wide, hyaline	Wide, hyaline	Wide, hyaline	Wide, hyaline
Submucosa	Thickened, eosinophils	Thickened, eosinophils	Thickened, eosinophils	Thickened, eosinophils	Thickened, eosinophils	Thickened, eosinophils
Musculature	Hypertrophied	Hypertrophied	Hypertrophied	Hypertrophied	Hypertrophied	Hypertrophied
Mucous glands	Numerous, distended, degenerated	Few, slight degenerative changes	Numerous, distended, degenerated	Numerous, distended, degenerated	Numerous, distended, degenerated	Numerous, distended, degenerated
Cartilage		Degeneration, fibrosis	Normal	Slight granular degeneration		Fibrous degeneration
Alveoli	Dilated, ruptured	Dilated, ruptured	Dilated, ruptured	Dilated, ruptured	Dilated, ruptured	Dilated, ruptured, atelectatic, bronchopneumonia
Arterioles						
	Extreme thickening	Moderate to extreme thickening	Slight to extreme thickening	Slight thickening	Normal	Moderate thickening
Heart						
Myocardium	Slight edema	Normal	Slight edema	Normal	Normal	Slight edema

* O L, Charcot-Leyden

† O, Curschmann

‡ This patient had ascites with 75 cc of fluid

degeneration varied from slight to great, and various degrees were noted in the same patient. Rarely was the basement membrane of the glands thickened like that of the bronchial mucosa. A widened submucosal layer was present in every instance, but it was not striking. In 3 instances degenerative changes in the bronchial cartilages were noted. Two patients had bronchopneumonia, and these were among the 4 who had had fever. In only 1 instance were areas of atelectasis present.

There was no important cardiac lesion in any of these patients. The hearts weighed from 200 to 365 Gm, the weight averaging 280 Gm. There was slight right-sided dilatation in 2 instances, but in none did the musculature of the right ventricle measure over 5 mm in thickness. Occasionally slight relative hypertrophy of the right side was noted. In no case was there significant valvular or coronary arterial disease, and microscopic sections showed no evidence of myocardial scarring.

In 5 of the 6 instances in which the abdomen was examined the liver was congested.

In no case was a relevant, significant pathologic condition found in other parts of the body.

The pertinent postmortem observations are summarized in table 2.

COMMENT

This, then, is a group of cases of bronchial asthma in which the patients apparently died as a direct result of the disease. As Alexander⁴ has stated, there is no single criterion for making a pathologic diagnosis of bronchial asthma. Every finding in asthma may be duplicated in some other pulmonary condition. However, asthma does produce a definite pathologic picture in the bronchial wall, described by Alexander as including (1) a widened basement membrane, (2) infiltration of eosinophils, (3) a widened submucosal layer, (4) hypertrophy of muscle and (5) "degenerative" mucous glands. In these 7 cases all these criteria were met, with the exception of the degenerative bronchial glands in the 2 instances in which the microscopic sections showed none. In addition, 6 of the patients had the characteristic thick, tenacious, elastic bronchial exudate, and all had a clinical picture consistent with asthma.

A few other microscopic lesions may be briefly discussed. Areas of atelectasis, as Huber⁵ pointed out, are a significant finding in that they indicate complete and persistent bronchial occlusion. Atelectasis has been infrequently mentioned in the literature and occurred in only 1 of this group of cases. As Huber stated, these areas are frequently sites

4 Alexander, H. L., in discussion on Michael, P. P., and Rowe, A. H. Pathology of Two Fatal Cases of Bronchial Asthma, *J. Allergy* 6:169 (Jan.) 1935.

5 Huber, H. L., in discussion on Michael, P. P., and Rowe, A. H. Pathology of Two Fatal Cases of Bronchial Asthma, *J. Allergy* 6:170 (Jan.) 1935.

TABLE 3—*Effect of Drugs*

	A D	L McD	B B	I B	R M	L K	G C
Previous response to epinephrine	Relief	Relief	Relief	Reaction	Relief	Relief	Not used
Dosage in hospital	Frequent, 0.1 to 1.0 cc	Frequent, 0.5 to 0.8 cc	Very frequent, 0.3 to 0.5 cc	5 injections, 0.1 to 0.3 cc	Very frequent, 0.5 cc	2 injections, 1.0 cc	2 injections 0.5 to 1.0 cc
Response	Diminishing relief	Diminishing relief	First relief, then failure	Slight	Diminishing relief	None	None
Atropine, dosage	0.25 mg, 20 injections in 2 months	0.25 to 0.3 mg, 64 injections in 21 days	None used	0.3 to 0.5 mg, 3 injections in 2 days	0.3 to 0.6 mg, 2 injections in 9 days	0.5 mg, 1 injection in 3 days	None used
Morphine, frequency of use	10 (10 days)	Almost to addiction	6 (6 days)	2 (2 days)	1 injection	None used	None used
Last dose, time ante mortem	9 hours	7 days	3 days	20 hours	9½ hours		
Digitalis, dose	4.1 Gm (13 days), digitalization	2.7 Gm (14 days), Nausea, stopped 4 days a m *	0.9 Gm (9 d ys), previous digitalization	7 minims q 5 h, none last 2 days	0.3 Gm (1 day), begun 1 day a m	None used	0.6 Gm digit this glucoside, last injection 1½ hours a m

* A m indicates ante mortem

for the subsequent development of pneumonia, and in several atelectatic areas in the lungs of our patient such a change had occurred

Another interesting observation is the finding of Charcot-Leyden crystals in the bronchial lumen. This occurred in 4 instances, and in 2 the crystals were large and abundant. This is apparently a rare occurrence, since a review of the descriptions of microscopic sections in the reported cases disclosed only 6, or possibly 7, instances in which the crystals had been seen. The possible seventh instance was described by Waldbott in the report of the case of an infant who had "some small spindle-shaped cells suggesting spores of fungi" in one of the bronchi.⁶ The crystals have the shape of two elongated hexagonal pyramids placed base to base (fig 3).⁷ Typical crystals within the lumen of a bronchus were reported by Berkart⁸ in 1889, by Monckeberg⁹ in 1909, by Marchand¹⁰ in 1916, by Dehner¹¹ in 1927, by Kountz and Alexander¹² in 1928 and by Antoniazzi¹³ in 1933.

The treatment of status asthmaticus is difficult, and the value of the therapeutic agents is uncertain. In this group each patient received a wide variety of drugs. Because four of these are of particular interest, the details of their administration are indicated in table 3.

It will be noted that 5 of the patients had previously obtained relief from epinephrine, 1 patient claimed to have had a severe reaction on the only occasion on which she had employed it and 1 patient allegedly had never used it. In the terminal illness the decreasing efficacy of epinephrine in relieving the symptoms was an important observation, for this made treatment extremely difficult. It is to be noted that the patient who had never previously received epinephrine gained no relief whatever from two injections. This suggests that a tolerance due to repeated administration of epinephrine may not be the reason for the patient's final failure to respond.

6 Waldbott, G. L. Pathologic Changes in Asthmatic Infants, *Am J Dis Child* **49** 1531-1539 (June) 1935

7 Thompson, J. H., and Paddock, F. K. The Significance of Charcot-Leyden Crystals, *New England J Med* **223** 936-939 (Dec) 1940

8 Berkart, J. I. B. *Bronchial Asthma*, London, J. & A. Churchill, 1889, cited by Huber, H. L., and Koessler, K. K. *The Pathology of Bronchial Asthma*, *Arch Int Med* **30** 689-760 (Dec) 1922

9 Monckeberg. Zur pathologischen Anatomie des Bronchialasthmas, *Verhandl d deutsch path Gesellsch* **14** 173, 1909

10 Marchand, F. Beitrag zur Pathologie und pathologischen Anatomie des Bronchialasthmas, *Beitr z path Anat u z allg Path* **61** 251, 1916

11 Dehner, W. Beitrag zur Pathologie des Asthma bronchiale, *Klin Wchn-schr* **6** 1412-1417 (July 23) 1927

12 Kountz, W. B., and Alexander, H. L. Death from Bronchial Asthma. Report of Three Cases, *Arch Path* **5** 1003-1019 (June) 1928

13 Antoniazzi, E. Un caso mortale di asma bronchiale, con autopsia, *Pol-clinico (sez med)* **40** 345-359 (June) 1933

Atropine was frequently employed in this series. Thieme and Sheldon¹ stated that atropine may have an untoward effect in cases of asthma by thickening the bronchial secretion, thus making it more difficult to raise the mucus plugs. In this connection it is noteworthy that the patient with the best developed Curschmann's spirals (twisted, compact, concentrated bronchial plugs) was the patient who had received twenty injections of atropine during her terminal illness. On the other hand, the 1 patient who had received more atropine than that had little mucus in the bronchial tree.

Many authorities¹⁴ have expressed the belief that morphine is contraindicated in status asthmaticus because it is a respiratory depressant. Most of the patients in this series received it, but a correlation between the time of death and the time of the last injection of morphine is not demonstrable. The last injection was administered nine, nine and a half and twenty hours and three and seven days, respectively, before death to the 5 patients receiving this drug.

Vaughan^{14a} has suggested that digitalis may be a dangerous drug in treatment of asthma. In support of this contention he cited the work of Wearn to the effect that digitalis reduces the output of the normal heart. He stated that he had seen a patient in status asthmaticus die shortly after digitalization, apparently as a result of the treatment. The patients in this series had essentially normal hearts except for occasional slight relative right-sided hypertrophy. Most of them received digitalis, and at least 3 were digitalized, but there is no correlation between the time of death and either the time of administration of digitalis or the amount given. On the basis of these data no conclusions can be drawn as to whether digitalis is harmful.

A partial explanation of the signs of cardiac failure occasionally observed was suggested by the remarkable gross appearance of the lungs *in situ*. As the chest plate was removed the lungs bulged out of their respective pleural cavities and over the mediastinum as if they had been confined under pressure. This must indicate at least a decreased negative pressure in the thorax and probably a positive pressure, since normally the lungs collapse as atmospheric pressure is established in the pleural space.

In support of such an interpretation are the observations of Smith, Harter and Alexander¹⁵ on anaphylactic shock in guinea pigs. With the onset of severe anaphylaxis the intrapleural pressure usually rose, after a

14 (a) Vaughan, W. T. *Practice of Allergy*, St. Louis, C. V. Mosby Company, 1939. (b) Rowe, A. H. *Clinical Allergy*, Philadelphia, Lea & Febiger, 1937. (c) Thieme and Sheldon¹.

15 Smith, F. R., Harter, J. S., and Alexander, H. L. *Observations on Circulation of Guinea Pigs During Bronchospasm*, *Proc. Soc. Exper. Biol. & Med.* **25**: 803 (June) 1928.

preliminary fall in 1 case to more than $+3$ mm of water from an initial level of -13 mm. The pressure within the right auricle gradually rose from $+5$ to $+70$ mm of water. The measurements tended to return to normal shortly before death. Though the change in intrapleural pressure was far from sufficient to give the effect of a tamponade, still it appears that in severe asthma the return of venous blood to the heart may be impeded. This may be a partial explanation of the frequently observed tachycardia.

In further support of this hypothesis are the observations of Alexander, Luten and Kountz,¹⁷ who reported increased venous pressure in 31 of 39 asthmatic patients. The method used gave readings of 5.0 to 5.5 cm of water in normal persons. In 31 of the 39 asthmatic patients the venous pressure ranged from 6.0 to 13.5 cm. These observations were usually made between attacks. During an attack the venous pressure was found to be elevated still further, though no figures were given. In the same group of patients there was no electrocardiographic evidence of right ventricular preponderance (1 exception) and usually no increase in the size of the heart. This appears to be additional evidence that in asthma the return of venous blood is impeded.

The similarity to the pressure relationships in constrictive pericarditis is obvious, though in asthma, of course, the signs are never so distinct.

It seems therefore not unreasonable to conclude that in severe status asthmaticus signs of right ventricular failure may sometimes appear and may be due entirely to extracardiac factors.

SUMMARY

The clinical and autopsy observations in the cases of 7 patients who died of bronchial asthma are reported.

The relationship between status asthmaticus and the signs of right-sided heart failure is discussed.

16 Footnote deleted by author.

17 Alexander, H. L., Luten, D., and Kountz, W. B. Effects on Heart of Long-Standing Bronchial Asthma, *J. A. M. A.* 88:882-884 (March 19) 1927.

Progress in Internal Medicine

DISEASES OF NUTRITION

REVIEW OF CERTAIN RECENT CONTRIBUTIONS

HUGH R BUTT, MD

AND

WILLIAM V LEARY, MD*

ROCHESTER, MINN

Within the past year vitamins again have been the main attraction in the study of nutrition. More and more evidence has accumulated to indicate that vitamins form an integral part of the enzyme system of the body and that clinical deficiencies of vitamins are usually multiple rather than singular. In addition, the broad aspect of national defense has again brought forward many timely discussions of national standards of nutrition and the controversial issue of fortification of foods. These general advances have been supplemented by numerous experimental and chemical contributions to knowledge of each separate vitamin, but space allows detailed discussion only of those of the greatest clinical significance.

VITAMIN A

Chemical and Physiologic Properties—It appears from recent reports that the chemical structure of vitamin (A_1) is closely related to that of vitamin A_2 . Most observations are in accord with the view that vitamin A_2 contains the same number of carbon atoms as vitamin A but differs in that it has one additional conjugated double bond¹. For the first time a fatty acid ester of vitamin A and also an alcohol of vitamin A were prepared in crystalline form².

Absorption studies on rats indicate that esters of vitamin A behave in the intestinal tract as do the esters of other fatty acids. Apparently they are hydrolyzed by the enzymes present, and during the height of absorption the vitamin exists in the intestinal wall chiefly as an alcohol. These facts, of course, argue against a major role for vitamin A in the

* Fellow in Medicine, the Mayo Foundation

From the Division of Medicine, the Mayo Clinic (Dr. Butt)

1 Gray, E. LeB., and Cawley, J. D. The Influence of Structure on the Elimination Maximum. I. The Structure of Vitamin A_2 , J. Biol. Chem. **143** 397-401 (June) 1940

2 Baxter, J. G., and Robeson, C. D. Crystalline Vitamin A Palmitate and Vitamin A Alcohol, Science **92** 203-204 (Aug. 30) 1940

absorption of fat³ Absorption of vitamin A by the tissues appears to be exceptionally rapid when it is administered intravenously Groth and Skurnik⁴ could not detect vitamin A in the urine of rabbits or men saturated with vitamin A administered in this manner

In an interesting study Clausen and his associates⁵ reported that after oral or intravenous administration of alcohol to dogs a sharp rise in the vitamin A content of the serum occurred Ethyl alcohol injected directly into the portal vein of 1 animal produced a marked rise in the vitamin A content of the blood in the hepatic vein This work was confirmed by Pett,⁶ who demonstrated that vitamin A is mobilized in the blood of human beings after injection of ethyl alcohol

It has long been known that carotene can be converted into vitamin A in the body It was suggested that this conversion takes place in the liver by means of an enzyme called "carotenase", it is believed generally that the liver plays an important role in regulating the distribution of vitamin A throughout the body In experiments on rats which were given injections of carotene in oil and killed at different times, With⁷ observed that the conversion of carotene to vitamin A took place almost entirely in the liver, this process began about two hours after an injection of carotene Similar experiments carried out with vitamin A disclosed that thirty to sixty minutes after an injection of carotene vitamin A can be identified in the liver

Perhaps the most interesting studies during the past year on the physiologic properties of vitamin A were made by Popper and his associates,⁸ who studied the distribution of vitamin A in the body This study was carried out by the fluorescence microscopic method, which permitted the visualization of vitamin A in tissue cells Popper^{8b} stated

3 Gray, E L , Morgareidge, K, and Cawley, J D Intestinal Absorption of Vitamin A in the Normal Rat, *J Nutrition* **20** 67-74 (July 10) 1940

4 Groth, H, and Skurnik, L Intravenous Saturation with Vitamin-A, *Acta med Scandinav* **101** 333-337, 1939

5 Clausen, S W , Baum, W S , McCoord, A B , Rydeen, J O , and Breese, B B Mobilization of Vitamin A from Its Stores in the Tissues by Ethyl Alcohol, *Science* **91** 318-319 (March 29) 1940

6 Pett, L B Mobilization of Vitamin A by Alcohol, *Science* **92** 63 (July 19) 1940

7 With, T K Investigations on Transformation of Carotene to Vitamin A in Liver of Rats, with Special Reference to Rate of Process, *Nord med (Hosptilstud)* **3** 2901-2903 (Sept 23) 1939

8 (a) Popper, H Histological Demonstration of Vitamin A in the Human Liver by Means of Fluorescence Microscopy, *Proc Soc Exper Biol & Med* **43** 234-236 (Feb) 1940, (b) Vitamin A The Distribution of Vitamin A in the Body, *J Mt Sinai Hosp* **7** 119-132 (Sept-Oct) 1940 (c) Popper, H, and Greenburg, R Distribution of Vitamin A in the Rat as Studied by Fluorescence Microscopy, *Am J Physiol* **129** 442 (May) 1940

that five years ago von Querner⁹ described fluorescent inclusions in the epithelial cells of the liver, the adrenal cortex and the pituitary gland, from which the fluorescence faded on irradiation. Popper maintained that the same fluorescence could be found in vitamin A concentrate and expressed the belief that this fluorescence of the tissue established the presence of vitamin A.

In ultraviolet light vitamin A has a characteristic green fluorescence which is used in the fluorescence microscopic method of demonstrating the presence of vitamin A in human and animal tissues.

Popper and his associates^{8c} carried out studies first on experimental animals. It was found that the liver of a normal rat contained large amounts of the characteristic green fluorescent substance, but the liver of a rat deficient in vitamin A showed none. However, if the deficient rats were fed vitamin A the typical fluorescence became visible. Popper and his associates observed further that the fluorescent substance was not vitamin A alone but rather small lipid droplets carrying the vitamin. In the intestine of the rat vitamin A could not be demonstrated, but after oral administration of vitamin A the fluorescence was seen in the lumen and within the wall of the duodenum and the upper portion of the jejunum.

It is interesting also that the retina of the rat contained considerable vitamin A in fine droplets and that even in the severe form of avitaminosis this material did not entirely disappear but seemed only to be reduced.^{8c} In fact, vitamin A was present in the retina of rats which died with avitaminosis and ulceration of the cornea.

Vitamins A (A_1) and A_2 also could be differentiated by the fluorescence microscopic method. Vitamin A_2 gave a brown-red, slowly fading fluorescence, instead of the green fluorescence common for vitamin A. Carotene also presented a type of fluorescence different from that of vitamin A_1 . When carotene was administered, the fluorescence characteristic of this compound appeared in the epithelial cells of the liver, the lungs and the kidneys. The intestine usually was free of the fluorescence characteristic of carotene after its administration. This observation led to the assumption that carotene is split in the endothelial cells of the intestine and especially in the Kupffer cells of the liver.

Popper with Greenburg also studied the distribution of vitamin A in human organs. It was found that the distribution of vitamin A in the human liver varied in amount even under normal conditions. In infants there was little storage of vitamin A in the liver, but in the fetus of about 5 months considerable amounts were present. Toward term these depots were reduced, and at birth only traces of vitamin A were distinct. Popper reported that it takes several years until the normal depots of

9 von Querner, F. R. Der mikroskopische Nachweis von Vitamin A im animalen Gewebe. Zur Kenntnis der paraplasmatischen Leberzeleinschlüsse. III, Klin. Wchnschr. 14 1213-1217 (Aug. 24) 1935.

vitamin A of the adult level are reached. In cases of generalized hepatic damage the storage of vitamin A was reduced, and in cases of such diseases as acute hepatitis or chronic atrophy of the liver only traces of vitamin A could be found. In cases of decompensated cirrhosis the liver was nearly free of vitamin A.

Tissues of the adrenal glands and lactating breasts of human beings were rich in vitamin A, but tissues from apparently normal kidneys, inactive breasts and the brain and the epithelium of the cornea, bronchi and urinary tract were found to be free of the vitamin. By the fluorescence microscopic technic, vitamin A was found in tumors which originated from a vitamin A—carrying mother tissue only.

We have described this work in some detail because it is felt that the fluorescence microscopic method offers rather widespread possibilities and it is hoped that in the near future other investigators will attempt to repeat and extend these efforts.

Vitamin A Requirements of Man—The definite minimal requirement of vitamin A of man is still unknown. In an extensive study, May and his associates¹⁰ found that normal, well nourished infants and children have levels of vitamin A in their blood which range from 5.5 to 27.3 units^{10a}. The levels of carotenoids in the blood of normal infants and children range from 3.1 to 75.7 units. These investigators observed that in patients with acute infections associated with fever the levels of both vitamin A and carotenoid in the blood were decreased. In such conditions, these low levels, however, should not be taken to indicate an inadequate intake of these substances or a depletion of their stores in the body.

Although most clinicians think that the average diet of the infant should be supplemented with vitamin A, Lewis and Haig¹¹ suggested that this is unnecessary. These authors reported that infants who received a diet low in vitamin A gained in weight just as well as, and were no more susceptible to infection than, those who received a diet high in vitamin A. From their observations it was concluded that 135 to 200 U. S. P. units of vitamin A, approximately 25 units per kilogram of body weight, covered the daily minimal requirement of vitamin A for the particular group of infants studied. They pointed out that because the average diet contains approximately twelve times as many

10 May, C. D., Blackfan, K. D., McCreary, J. F., and Allen, F. H., Jr. Clinical Studies of Vitamin A in Infants and in Children, *Am. J. Dis. Child.* **59** 1167-1184 (June) 1940.

10a The values are expressed, not in U. S. P. units, but abstract units directly related to the galvanometer readings on the Evelyn colorimeter, as described by May (page 1170¹⁰).

11 Lewis, J. M., and Haig, C. Vitamin A Requirements in Infancy as Determined by Dark Adaptation, *J. Pediat.* **15** 812-823 (Dec.) 1939, correction, *ibid.* **16** 274 (Feb.) 1940.

units of vitamin A as the diet low in vitamin A which they used, there is a large margin of safety in the average infant's diet with respect to content of vitamin A.

In a further study of minimal requirements of vitamin A of normal adults, Booher and Callison¹² found that a daily intake of approximately 47 and 57 U S P units, respectively, of vitamin A per kilogram of body weight was necessary for the maintenance of normal dark adaptation in 2 normal adults when the vitamin A in the diet was derived almost entirely from the carotene in cooked green peas. They observed that the utilization of the vitamin A of cooked peas was better than that of vitamin A of cooked spinach. They further demonstrated that administration of thiamine hydrochloride, riboflavin or dietary fats in large quantities in addition to carotene did not have beneficial effects on the utilization of carotene by these normal adults.

In a special article published by the Council on Foods of the American Medical Association, Dornbush and his associates¹³ described a study of the content of carotene and vitamin A in milk marketed by eight large distributors in the Madison and the Milwaukee areas of Wisconsin. They observed that all milk had seasonal changes in content of both carotene and vitamin A, the seasonal changes in carotene were greater than those in vitamin A. Milk was fairly constant in vitamin potency per gram of butter fat. The market milk (mainly Holstein) supplied from January to April averaged 327 micrograms, or 1,088 U S P units, of vitamin A per quart.

Methods of Measuring Vitamin A Deficiency—Whether deficiency of vitamin A in man can be measured by testing adaptation to dark continues to be a controversial subject. Several groups of investigators¹⁴ contended that this method is satisfactory for measuring deficiency of vitamin A in man. Steininger and Roberts,¹⁵ however, contended that

12 Booher, L. E., and Callison, E. C. The Minimum Vitamin-A Requirements of Normal Adults, the Utilization of Carotene as Affected by Certain Dietary Factors and Variations in Light Exposure, *J. Nutrition* **18** 459-471 (Nov) 1939.

13 Dornbush, A. C., Peterson, W. H., and Olson, F. R. The Carotene and Vitamin A Content of Market Milks, *J. A. M. A.* **114** 1748-1751 (May 4) 1940.

14 Steele, E. J. P. Effect of Vitamin-A Therapy Estimated by a Rapid Optical Test, *Lancet* **2** 205-206 (Aug 17) 1940. Sheftel, A. G. Dark Adaptation and Vitamin A Deficiency. A New Technic, *Am. J. Clin. Path.* **10** 168-175 (Feb) 1940. Pett, L. B. Vitamin A Deficiency. Its Prevalence and Importance as Shown by a New Test, *J. Lab. & Clin. Med.* **25** 149-160 (Nov) 1939. Blanchard, E. L., and Harper, H. A. Measurement of Vitamin A Status of Young Adults by the Dark Adaptation Technic, *Arch. Int. Med.* **66** 661-669 (Sept) 1940. McDonald, R., and Adler, F. H. Effect of Anoxemia on the Dark Adaptation of the Normal and of the Vitamin A-Deficient Subject, *Arch. Ophth.* **22** 980-988 (Dec) 1939.

15 Steininger, G., and Roberts, L. J. Biophotometer Test as an Index of Nutritional Status for Vitamin A, *Arch. Int. Med.* **64** 1170-1186 (Dec) 1939.

although some relation exists between the biophotometric readings and vitamin A nutrition, the relation is not close enough to warrant the use of the test as a means of diagnosing subclinical deficiency of vitamin A. These authors pointed out that the method was time consuming and that for this reason its routine clinical use was practically excluded. Harris and Abbasy¹⁶ expressed a similar opinion, and Isaacs and her associates¹⁷ emphasized that significance should not be attached to minor fluctuations in dark adaptation in terms of deficiency of vitamin A unless statistical methods are used to test the reliability of the differences. It is true that a majority of workers have concluded that the study of dark adaptation can be used as a test for deficiency of vitamin A, but Thomson and his associates¹⁸ pointed out that until differences in technic and interpretation of results have been resolved it will be impossible to ascertain how far recorded observations represent physiologic facts.

In a study of children, Baum and McCoord¹⁹ did not find any correlation between biophotometric readings and the content of vitamin A in the blood of 98 untraumatized subjects. They pointed out that a single reading on the biophotometer was not of value in estimating deficiency of vitamin A and that readings obtained by frequent testing with the biophotometer did not correlate with the vitamin A value of blood of these particular subjects. Several other groups of investigators studied the level of vitamin A in the blood of normal adults.²⁰ Steininger and her associates^{20a} studied the level of vitamin A in the blood of 4 normal

16 Harris, L. J., and Abbasy, M. A. The Dark-Adaptation Test: Its Reliability as a Test for Vitamin-A Deficiency, *Lancet* **2** 1299-1305 (Dec. 23) and 1355-1359 (Dec. 30) 1939.

17 Isaacs, B. L., Jung, F. T., and Ivy, A. C. Clinical Studies of Vitamin A Deficiency. Biophotometer and Adaptometer (Hecht) Studies on Normal Adults and on Persons in Whom an Attempt Was Made to Produce Vitamin A Deficiency, *Arch. Ophth.* **24** 698-721 (Oct.) 1940.

18 Thomson, A. M., Griffith, H. D., Mutch, J. R., Lubbock, D. M., Owen, E. C., and Logaras, G. A Study of Diet in Relation to Health. Dark Adaptation as an Index of Adequate Vitamin A Intake, III. The Relation of Diet to Rate and Extent of Dark Adaptation, *Brit. J. Ophth.* **23** 697-723 (Nov.) 1939.

19 Baum, W. S., and McCoord, A. B. The Relationship Between Biophotometer Tests and the Vitamin A Content of the Blood of Children, *J. Pediat.* **16** 409-418 (April) 1940.

20 (a) Steininger, G., Roberts, L. J., and Brenner, S. Vitamin A in the Blood of Normal Adults. The Effect of a Depletion Diet on Blood Values and Biophotometer Readings, *J. A. M. A.* **113** 2381-2387 (Dec. 30) 1939. (b) Pett, L. B., and LePage, G. A. Vitamin A Deficiency. III. Blood Analysis Correlated with a Visual Test, *J. Biol. Chem.* **132** 585-593 (Feb.) 1940. (c) French, R. B. Assay of Vitamin A with the Photoelectric Colorimeter, *Indust. & Engin. Chem. (Analyt. Ed.)* **12** 351-352 (June) 1940. (d) Kimble, M. S. The Photocolorimetric Determination of Vitamin A and Carotene in Human Plasma, *J. Lab. & Clin. Med.* **24** 1055-1065 (July) 1939.

subjects who lived on a vitamin A depletion diet for two to four months. The results suggested that although the amount of vitamin A in the blood of fasting persons is dependent on the amount contained in the diet, evidence as to whether the determinations of vitamin A in the blood are of value in judging the nutritional status of man is still contradictory.

From these studies it can be judged that the methods for measuring vitamin A deficiency in man are still somewhat unreliable and further investigation is needed. Some chemists still doubt whether the small quantities of vitamin A present in the blood stream of man can be measured by the chemical methods now available. Others feel that a satisfactory chemical method cannot be developed until the capacity of the body for storing vitamin A can be estimated to some degree.

Role of Vitamin A in Health and Disease—Inability to absorb vitamin A in a normal manner exists in cases of celiac disease,²¹ catarrhal jaundice²² and various diseases of the liver in which the flow of bile is disrupted. Breese, McCoord and Salah²³ stressed the importance of considering this physiologic fact in the treatment of these diseases.

Straumfjord²⁴ concluded that vernix caseosa is a manifestation of a deficiency of vitamin A in the newborn and that it represents disturbances in cornification analogous to the cutaneous changes accompanying keratomalacia and other manifestations of deficiency of vitamin A. This author administered 50,000 to 100,000 or more U S P units of vitamin A daily to 25 pregnant mothers for six months or more. Twenty-one babies born to these 25 mothers had little or no vernix, 4 babies had moderate or much vernix. To another group of 29 mothers, less than 50,000 U S P units of vitamin A was administered daily for six months or more. Fourteen of the babies born to this group of mothers had little or no vernix, and 15 were born with moderate or much vernix. Lehman and Rapaport²⁵ described cutaneous manifestations of deficiency of vitamin A in children. These authors obtained maximal improvement of the skin with daily doses of 100,000 to 300,000 international units of vitamin A given over two or three months. They expressed the belief that keratosis pilaris, ichthyosis follicularis and other synonyms were descriptive terms for the cutaneous manifestations of

21 Breese, B. B., Jr., and McCoord, A. B. Vitamin A Absorption in Celiac Disease, *J. Pediat.* **15** 183-196 (Aug.) 1939.

22 (a) Breese, B. B., and McCoord, A. B. Vitamin A Absorption in Catarrhal Jaundice, *J. Pediat.* **16** 139-145 (Feb.) 1940. (b) Salah, M. Vitamin A Deficiency in Jaundice, *J. Egyptian M. A.* **23**:153-161 (March) 1940.

23 Breese and McCoord (footnotes 21 and 22a). Salah^{22b}.

24 Straumfjord, J. V. Vernix Caseosa. A Manifestation of Vitamin A Deficiency, a Preliminary Report, *West J. Surg.* **48** 341-351 (June) 1940.

25 Lehman, E., and Rapaport, H. G. Cutaneous Manifestations of Vitamin A Deficiency in Children, *J. A. M. A.* **114** 386-393 (Feb. 3) 1940.

deficiency of vitamin A. Other investigators²⁶ suggested that vitamin A exerted a favorable effect on the nutrition of the intestinal lining and was, therefore, of some use in the treatment of typhoid among children.

Accumulated evidence continues to indicate that the liver plays a major role in the metabolism of vitamin A. Jensen and With²⁷ and others²⁸ found extremely low concentrations of vitamin A and carotene in the livers of the patients who had cirrhosis. Low concentrations of vitamin A in the liver also have been observed among patients with dysentery,²⁸ tuberculosis²⁹ or various hepatic disorders³⁰.

Brazer and Curtis³¹ carried out a rather extensive study of the metabolism of vitamin A in cases of juvenile diabetes mellitus. These investigators observed 20 patients who had diabetes mellitus and normal ocular fundi but who, as determined by biophotometric readings, had a suggestive deficiency of vitamin A in spite of the fact that the levels of carotene in the blood were above normal. Three of these 20 patients gave a history of night blindness, and 9 showed clinical evidence of mild deficiency of vitamin A as exemplified by various cutaneous changes. An increase in the already high values for carotene in the blood occurred after administration of large doses of carotene, but the biophotometric readings failed to indicate improvement. Large amounts of vitamin A given over a similar period, however, produced significant improvement as measured by the biophotometric readings. It was observed that if the large doses of vitamin A were removed from the diet of patients whose biophotometric readings were held at normal or nearly normal by these doses, an immediate relapse of the biophotometric readings to subnormal value occurred. Levels of carotene in the blood in 90 per cent of these 20 patients with diabetes mellitus were above normal. Administration of 60,000 U. S. P. units of vitamin A in the form of crystalline carotene dissolved in a vegetable oil given for fourteen days

26 Giraud, P., and Vallette, A. Essai de traitement de la fièvre typhoïde chez l'enfant par la vitamine A, *Arch de méd d enf* **42** 691-697 (Nov-Dec) 1939, abstracted, *J A M A* **114** 832-833 (March 2) 1940.

27 Jensen, H. B., and With, T. K. Vitamin A and the Carotenoids in the Liver of Mammals, Birds, Reptiles and Man with Particular Regard to the Intensity of the Ultraviolet Absorption and the Carr-Price Reaction of Vitamin A, *Biochem J* **33** 1771-1786 (Nov) 1939.

28 Woo, T. T., and Chu, F. T. The Vitamin A Content of the Livers of Chinese Infants, Children and Adults, *Chinese J Physiol* **15** 83-100 (Jan 30) 1940.

29 Crimm, P. D., and Short, D. M. Vitamin A Content of the Human Liver in Tuberculosis, *Ann Int Med* **13** 61-63 (July) 1939.

30 Wohl, M. G., and Feldman, J. B. Vitamin A Deficiency in Disease of the Liver. Its Detection by Dark-Adaptation Method, *J Lab & Clin Med* **25** 485-494 (Feb) 1940.

31 Brazer, J. G., and Curtis, A. C. Vitamin A Deficiency in Diabetes Mellitus, *Arch Int Med* **65** 90-105 (Jan) 1940.

did not affect light adaptation of the patients with this condition, but the daily administration of 60,000 U S P units of vitamin A in the form of concentrated fish liver oil increased their light adaptation in three to twenty-one days. The authors suggested that poor adaptation to light among patients who have juvenile diabetes mellitus might result from an inability to convert carotene into vitamin A.

The uses and requirements of vitamin A in a variety of other diseases have also been reported during the past year. Hall and his associates³² did not observe obvious clinical improvements after administration of large doses of vitamin A to patients who had rheumatoid arthritis. In a preliminary report, asthenopia was considered the result of deficiency of vitamin A.³³ One author suggested the local application of vitamin A in cases of corneal inflammation,³⁴ another author³⁵ demonstrated experimentally the lack of evidence of the local action of vitamin A.

THIAMINE (VITAMIN B₁)

Chemical and Physiologic Properties—Much work on the relation of thiamine to the metabolism of pyruvic acid was carried out during the past year. Platt and Lu³⁶ observed that in human subjects elevated levels of blood pyruvate were often associated with deficiency of thiamine. They also found that the initial level of blood pyruvate was a definite indication of the degree of deficiency in cases of beriberi. In such cases several hours were required after the administration of thiamine before the accumulated pyruvate was removed from the blood. Only 5 mg of thiamine hydrochloride was needed to restore the normal metabolism of pyruvic acid in cases of severe beriberi. Further studies by these authors³⁷ demonstrated that light muscular work by patients who were deficient in thiamine was followed by an increased level of pyruvate in the blood and increased urinary excretion of pyruvic acid. Values for blood pyruvate as high as those found in cases of fulminating beriberi

32 Hall, M. G., Bayles, T. B., and Soutter, P. Vitamin A Requirements in Rheumatoid Arthritis, *New England J. Med.* **223** 92-96 (July 18) 1940.

33 Cordes, F. C., and Harrington, D. O. Asthenopia Due to Vitamin-A Deficiency, *Am. J. Ophth.* **22** 1343-1354 (Dec.) 1939.

34 de Grósz, S. Local Use of Vitamin A Preparations in Ophthalmic Practice, *Arch. Ophth.* **22** 727-734 (Nov.) 1939.

35 de Roth, A. Local Action of Oils Containing Vitamin A. Experimental Contribution, *Arch. Ophth.* **24** 281-291 (Aug.) 1940.

36 Platt, B. S., and Lu, G. D. Studies on the Metabolism of Pyruvic Acid in Normal and Vitamin B₁ Deficiency States. IV. The Accumulation of Pyruvic Acid and Other Compounds in Beri-Beri and the Effect of Vitamin B₁, *Biochem. J.* **33** 1525-1537 (Oct.) 1939.

37 Lu, G. D., and Platt, B. S. Studies on the Metabolism of Pyruvic Acid in Normal and Vitamin B₁ Deficiency States. V. The Effect of Exercises on Blood Pyruvate in Vitamin B₁ Deficiency in Man, *Biochem. J.* **33** 1538-1543 (Oct.) 1939.

were occasionally attained after exercise by deficient patients, but among normal patients the blood pyruvate usually returned to a normal level after half an hour of rest. These authors³⁷ expressed the belief that the increase in bisulfite-binding substances in patients who had beriberi was greater than could be accounted for by pyruvic acid alone, because the content of pyruvic acid in the blood frequently can be restored to normal while at the same time only a slight reduction in the bisulfite-binding substances takes place. On the other hand, Robinson and his associates³⁸ found the bisulfite-binding substances increased in 7 of 26 cases in which excretion of thiamine in the urine was normal. In 7 of 16 cases in which the concentration of thiamine in the urine was indicative of thiamine subnutrition the levels of bisulfite-binding substances were normal. One patient was on a diet inadequate in thiamine for twenty-two days, in this period urinary excretion of thiamine decreased to a low level, yet there was no increase of the bisulfite-binding substances in the blood. From these investigations the authors concluded that the determination of the bisulfite-binding substances in the blood lacked sensitivity as a means of detecting latent or mild forms of deficiency of thiamine.

Another interesting phenomenon resulting from the administration of thiamine to experimental animals was reported by Engel and Phillips³⁹. These authors demonstrated that when thiamine hydrochloride was administered to chicks or rats deficient in thiamine hydropic degeneration and fatty metamorphosis occurred in the parenchyma of the hepatic cells. This histologic reaction in the liver of chicks was not prevented by administration of choline or by diets high in casein. Desiccated thyroid, however, was effective in preventing histologic reactions in the livers of both animals. Chemical analysis of the livers of these animals disclosed an increase in total fat, glycogen and moisture, but no change in the content of phospholipid or protein. It was observed also that hepatic degeneration did not occur after administration of thiamine if the animals were not allowed to eat.

Evidence was presented which suggested that animals deficient in calcium were incapable of utilizing the thiamine available in their diet.⁴⁰ Sinclair⁴¹ found thiamine in extremely small amounts in cerebrospinal fluid but expressed the belief that estimation of the substance in the

38 Robinson, W. D., Melnick, D., and Field, H., Jr. Correlation Between the Concentration of Bisulphite Binding Substances in the Blood and the Urinary Thiamin Excretion, *J. Clin. Investigation* **19** 483-488 (May) 1940.

39 Engel, R. W., and Phillips, P. H. Fatty Livers as a Result of Thiamin Administration and the Vitamin B₁ Deficiency of the Rat and the Chick, *J. Nutrition* **18** 329-338 (Oct. 10) 1939.

40 Badger, L. F., and Masunaga, E. Possible Relation of Calcium Deficiency to the Utilization of Vitamin B₁, *Pub. Health Rep.* **54** 1775-1779 (Sept. 29) 1939.

41 Sinclair, H. M. The Estimation of Vitamin B₁ in Cerebrospinal Fluid, *Biochem. J.* **33** 1816-1821 (Nov.) 1939.

fluid was useless for clinical purposes. The highest values were obtained in cases of meningitis and of cerebral abscess.

Methods of Measuring Vitamin B₁ and the Requirement of the Normal Person—Some excellent studies were carried out in this particular field. Melnick and his associates⁴² observed that a considerable part of the thiamine hydrochloride which was taken into the stomach of a fasting person was destroyed prior to absorption and that if it was given parenterally, most of it was excreted in the urine in the first four hours. Women were found to excrete much less thiamine than men, and the volume of urine appeared to be an insignificant factor in governing the urinary excretion of thiamine. Ninety micrograms for males and 60 micrograms for females were established as the normal minimal values of thiamine excreted in a twenty-four hour sample of urine. Values below these levels were considered to be evidence of a possible deficiency of thiamine. The thiamine in the urine of a person subsisting on a diet deficient in vitamin B₁ for thirty-two days for investigative purposes decreased from normal to a level characteristic of avitaminosis. Although low urinary excretion is significant, it apparently does not indicate a deficiency in the vitamin, as it may mean that the patient's diet has recently been deficient in thiamine. However, if the patient was given a normal diet a few days prior to and during the day of the test and still a small amount of the vitamin was excreted, deficiency was considered to be present. It was observed that two weeks were required before urinary excretion of thiamine returned to the basal level after the patient had been taking a deficient diet. Borson⁴³ used a modification of the thiochrome reaction for the chemical assay of thiamine in the urine and observed that normal persons excreted 100 to 300 micrograms daily. He expressed agreement with Melnick and his associates⁴² that the efficiency of utilization of thiamine depended in part on the degrees of absorption and excretion, that is, large doses administered orally are absorbed incompletely and large doses administered parenterally are excreted rapidly. Therefore, small frequent doses are utilized most efficiently.

Several other investigators⁴⁴ found somewhat similar levels of excretion of thiamine among normal subjects. In some cases of diffuse

42 Melnick, D., Field, H., Jr., and Robinson, W. D. A Quantitative Chemical Study of the Urinary Excretion of Thiamine by Normal Individuals, *J. Nutrition* **18** 593-610 (Dec.) 1939.

43 Borson, H. J. Clinical Application of the Thiochrome Reaction in the Study of Thiamin (Vitamin B₁) Deficiency, *Ann. Int. Med.* **14** 1-27 (July) 1940.

44 Wang, Y. L., and Harris, L. J. Methods for Assessing the Level of Nutrition of the Human Subject. Estimation of Vitamin B₁ in Urine by the Thiochrome Test, *Biochem. J.* **33** 1356-1369 (Aug.) 1939. Sinclair, H. M. The Estimation of Vitamin B₁ in Blood. II. A Further Modification of Meiklejohn's Method, *ibid.* **33** 2027-2036 (Dec.) 1939. Wright, M. D., and Baker, A. Z. Vitamin B₁ Excretion on a Varied Intake, *J. Hyg.* **39** 638-642 (Nov.) 1939.

hepatic damage,⁴³ excretion of thiamine was much higher than is considered normal, but in cases of clinical diabetes mellitus a particular unsaturation of thiamine was not observed.⁴⁵ In cases of "alcoholic beriberi," also, abnormally low excretion of thiamine in the urine was observed.⁴⁶ In a study carried out in China, Hou and Yang⁴⁷ did not observe excretion of thiamine in the urine of patients who had beriberi. On the other hand, Pannekoek-Westenburg and van Veen⁴⁸ observed divergent values for thiamine in the blood in 19 cases of manifest beriberi. In 9 of these 19 cases values were low, but in some of the cases of severe beriberi they were normal. The blood levels of thiamine in a majority of 165 cases of nutritional edema and in all but 2 of 19 cases of polyneuritis of various origins were within the normal range. On the basis of these rather extensive observations, the authors concluded that the determination of thiamine in the blood is not yet of great practical importance. Goodhart and Sinclair⁴⁹ presented evidence which demonstrated that the amount of cocarboxylase in the blood as determined by chemical methods varied directly with the amount of total thiamine as determined by biologic methods and also with the degree of saturation of the tissues with the vitamin. In most clinical cases, the determination of the amount of cocarboxylase in the blood provided a rapid and reliable method of estimating the degree of saturation of the tissues with the vitamin.

Many other methods for the chemical determination of thiamine in the urine of man also were described.⁵⁰

45 Pollack, H., Dolger, H., Ellenberg, M., and Cohen, S. A Test Proposed to Measure Vitamin B₁ Saturation in Humans, *Proc Soc Exptl Biol & Med* **44** 98-100 (May) 1940.

46 Robinson, W. D., Melnick, D., and Field, H., Jr. Urinary Excretion of Thiamin in Clinical Cases and the Value of Such Analyses in the Diagnosis of Thiamin Deficiency, *J Clin Investigation* **19** 399-408 (March) 1940.

47 Hou, H. C., and Yang, E. F. Observations on Vitamin B₁ Metabolism. I. Urinary Excretion by Normal Individuals and Beriberi Patients, *Chinese J Physiol* **14** 269-282 (Sept 30) 1939.

48 Pannekoek-Westenburg, S. J. E., and van Veen, A. G. Vitamin B₁ Content of Blood in Healthy Persons and Patients, *Geneesk tijdschr v Nederl-Indie* **80** 1773-1820 (July 23) 1940, abstracted, *J A M A* **115** 1494 (Oct 26) 1940.

49 Goodhart, R., and Sinclair, H. M. Deficiency of Vitamin B₁ in Man as Determined by the Blood Cocarboxylase, *J Biol Chem* **132** 11-21 (Jan) 1940.

50 Pollack, H., Dolger, H., Ellenberg, M., and Cohen, S. Test for the Rapid Estimation of Vitamin B₁ Saturation, *J Clin Investigation* **19** 771 (Sept) 1940. Emmett, A. D., Peacock, G., and Brown, R. A. Chemical Determination of Thiamine by a Modification of the Melnick-Field Method, *J Biol Chem* **135** 131-138 (Aug) 1940. Hills, G. M. The Thiochrome Test for Aneurin (Vitamin B₁) in Urine as an Index of Nutritional Level, *Biochem J* **33** 1966-1979 (Dec) 1939. Ferrebee, J. W., and Carden, G. A. A Procedure for the Routine Determination of Vitamin B₁ in Urine, *J Lab & Clin Med* **25** 1320-1324 (Sept) 1940. Melnick, D., and Field, H., Jr. Chemical Determination, Stability, and Form of Thiamine in Urine, *J Biol Chem* **130** 97-107 (Sept) 1939.

Clinical Deficiencies of Thiamine—Deficiency of thiamine has been induced in human beings by several investigators⁵¹ The symptoms of deficiency usually appear in three to six weeks Chemical evidence of the deficiency usually is characterized by aching of the muscles of the calf and achilles tendons and by paresthesia of the lower extremities Marked fatigue, lassitude, anorexia, burning of the feet, dyspnea on exertion, palpitation, constipation, loss of weight and absence, of, or decrease in, gastric acidity are also noted Abnormality is evidenced in the electrocardiograms In this direction the study by Elsom and his associates^{51d} is particularly interesting These authors reported a study made on 1 person who voluntarily consumed for four months a constant diet deficient only in the vitamin B complex In general, clinical metabolic changes were evident after five weeks, but they were not striking until the end of eight weeks Edema appeared early in the deficiency, and loss of weight occurred late The clinical and metabolic changes responded in part to thiamine hydrochloride, were influenced only slightly by thiamine hydrochloride and riboflavin and were relieved by the administration of brewers' yeast The main changes were in the carbohydrate metabolism During the deficiency, the blood sugar failed to return to normal limits within three to four hours after ingestion of dextrose This effect disappeared only after administration of yeast The bisulfite-binding power of the blood during deficiency was not increased, but after ingestion of dextrose the values for pyruvic acid were elevated and remained high for four hours or until thiamine hydrochloride was administered The value for lactic acid in the blood was elevated during the deficiency and also returned to normal after the administration of thiamine hydrochloride

Considerable investigation of the effect of thiamine in treatment of various neurologic disorders has continued, but the exact relation of thiamine to the metabolism of nerve tissue is still incompletely understood This enigma is again voiced in an interesting article by Meiklejohn,⁵² who asked, "Is thiamine the antineuritic vitamin?" From the

51 (a) Jolliffe, N., Goodhart, R., Gennis, J., and Cline, J. K. The Experimental Production of Vitamin B₁ Deficiency in Normal Subjects. The Dependence of the Urinary Excretion of Thiamin on the Dietary Intake of Vitamin B₁, *Am J M Sc* **198** 198-211 (Aug.) 1939 (b) Williams, R. D., Mason, H. L., and Smith, B. F. Induced Vitamin B₁ Deficiency in Human Subjects, *Proc Staff Meet, Mayo Clin* **14** 787-793 (Dec. 13) 1939 (c) Williams, R. D., Mason, H. L., and Wilder, R. M. Experimental Vitamin B₁ Deficiency in Man, *J Nutrition (supp)* **19** 7 (June) 1940 (d) Elsom, K. O., Lukens, F. D. W., Montgomery, E. H., and Jonas, L. Metabolic Disturbances in Experimental Human Vitamin B₁ Deficiency, *J Clin Investigation* **19** 153-161 (Jan.) 1940 (e) Melnick, Field and Robinson⁴²

52 Meiklejohn, A. P. Is Thiamin the Antineuritic Vitamin? *New England J Med* **223** 265-273 (Aug. 22) 1940

experimental side he pointed out that although it is possible that chronic, though partial, deficiency of thiamine may result in true polyneuritis, this does not appear to have been adequately demonstrated as yet. Furthermore, in his study he found no clear experimental evidence that true anatomic polyneuritis in animals can be cured by thiamine hydrochloride, for these and for other reasons, he concluded that so far as the evidence from the laboratory is concerned there is really no great justification for referring to thiamine as the antineuritic vitamin. Because the chemical identification of thiamine was not made until 1936, Meiklejohn⁵² expressed the opinion that any article prior to this date in which specific claims were made for the etiologic relation of thiamine deficiency to nutritional polyneuritis cannot be cited without reservations. He correctly pointed out that the failure to appreciate this fact has led to several misrepresentations in recent articles. In a careful analysis of the literature since synthetic thiamine hydrochloride first became available for clinical use, Meiklejohn⁵² found considerable lack of evidence concerning the use of thiamine hydrochloride in the treatment of polyneuritis. In most instances the composition and type of diet were not mentioned, and in many instances other members of the vitamin B complex were given. The possibility, therefore, of other dietary factors contributing to the observed response cannot be excluded. The evidence throughout seems to rest mainly on the relief by administration of thiamine hydrochloride of the symptoms of pain, weakness and inability to walk. In some unpublished data, Meiklejohn⁵² has observed that thiamine hydrochloride without other medication may have a marked effect in the relief of muscular pain in tender calves occurring in cases of nutritional polyneuritis, but in the cases observed by him there was no associated improvement in the objective neurologic signs, and certainly the relief of the pain cannot be taken as evidence of improvement of the neuritis.

Meiklejohn⁵² stated that polyneuritis associated with alcoholism, pregnancy and gastrointestinal disturbances is unquestionably due to nutritional deficiency and is in every way similar to the polyneuritis of oriental beriberi. But he commented as follows:

When the literature of the last ten years is considered in perspective, the conclusion is inescapable that thiamin has never deserved the title of "antineuritic vitamin," and has not yet shown itself capable of filling completely the role that was formerly assigned to the hypothetical antiberiberi vitamin.

The exact deficiency responsible for nutritional neuritis remains obscure. Quite probably it is usually a multiple deficiency involving several dietary factors, of which thiamin may be one. But there is still a possibility that the true antineuritic vitamin has yet to be discovered.

For these reasons he suggested, as did many others, that the treatment of polyneuritis should include "an ample and nutritious diet,

together with the administration of such preparations as yeast and crude liver extract to ensure an adequate supply of the entire vitamin B complex "

Aring and Spies⁵³ expressed the belief that the rapid relief of discomfort in neuritis of man probably results from the humoral nature of the vitamin, but that lack of thiamine alone is not the specific cause of nutritional neuritis. They recommended the parenteral administration of at least 50 to 100 mg of thiamine hydrochloride each day, in several doses of 10 to 20 mg each. It is their belief that if a response is not obtained in a week further treatment with thiamine hydrochloride will be unavailing. From a study based on 520 patients traced for five years, Vorhaus⁵⁴ attempted to evaluate the use of thiamine hydrochloride in the treatment of polyneuritis. He reported that the shorter the duration of symptoms, the quicker the response in most instances. Approximately 75 per cent of his patients revealed some improvement within four weeks.

It has been suggested recently that delirium tremens is essentially a condition of deficiency of thiamine. Investigators⁵⁵ observed that when thiamine hydrochloride was given intravenously, even in the presence of continued drinking, symptoms of delirium tremens disappeared. In cases of Korsakoff's psychosis, however, improvement was not noted after administration of thiamine hydrochloride⁵⁶. In 20 patients who had severe, moderately severe and mild forms of Sydenham's chorea, marked improvement was noted after administration of the vitamin B complex⁵⁷. It was noted also in animals⁵⁸ that the abstinence symptoms of morphine addiction were markedly decreased after administration of thiamine hydrochloride. Similar reports on clinical material have not yet appeared.

Bakhsh⁵⁹ reported the cases of 7 patients with trigeminal neuralgia to whom thiamine hydrochloride was given in doses of 10 to 30 mg

53 Aring, C D, and Spies, T D. A Critical Review. Vitamin B Deficiency and Nervous Disease, *J Neurol & Psychiat* **2** 335-360 (Oct) 1939

54 Vorhaus, M G. Evaluation of Vitamin B₁ (Thiamin Chloride) in the Treatment of Polyneuritis, *Am J M Sc* **198** 837-844 (Dec) 1939

55 Kiene, H E, Streitwieser, R J, and Miller, H. The Role of Vitamin B₁ in Delirium Tremens, *J A M A* **114** 2191-2194 (June 1) 1940

56 Bowman, K M, Goodhart, R, and Jolliffe, N. Observations on the Role of Vitamin B₁ in the Etiology and Treatment of Korsakoff Psychosis, *J Nerv & Ment Dis* **90** 569-575 (Nov) 1939

57 Stone, S. Treatment of Sydenham's Chorea by Fever and Vitamin B Therapy, *New England J Med* **223** 489-496 (Sept 26) 1940

58 Fitzhugh, O G. The Effect of Vitamin B₁ on Morphine Abstinence Symptoms, *J Pharmacol & Exper Therap* **67** 423-428 (Dec) 1939

59 Bakhsh, I. Treatment of Nervous Diseases by Vitamin B₁ with Special Reference to Trigeminal Neuralgia. A Report of Seven Cases, *Indian M Gaz* **74** 456-458 (Aug) 1939

daily Four patients experienced complete relief, and 2, partial relief, 1 patient was unaffected The 4 patients whose relief of pain was dramatic began to improve within forty-eight hours after administration of thiamine hydrochloride Others⁶⁰ observed relief of pain in neuritis of the eighth cranial nerve after administration of thiamine hydrochloride

Equivocal results have been reported after the administration of thiamine hydrochloride to patients who had functional digestive disturbances,⁶¹ multiple sclerosis,⁶² dysphagia⁶³ or acrodynia⁶⁴

After administration of thiamine hydrochloride in doses of 5 mg three times a day, Ochsner and Smith⁶⁵ observed marked relief of pain among patients who had varicose ulcers The authors reported that if the symptoms do not subside within three to four days the dose should be doubled Owens and his associates⁶⁶ made a critical study of vitamin B therapy for patients who have diabetes mellitus In contradistinction to several claims made during the past year in which vitamin therapy was said to be of some benefit to patients with diabetes, these investigators pointed out that the administration of large amounts of thiamine hydrochloride and riboflavin in cases of well controlled diabetes over many weeks did not reduce the insulin requirement or alter in any way the severity of the diabetic state The authors concluded that in cases of well controlled diabetes, except in those of diabetes mellitus, use of any thiamine hydrochloride or riboflavin beyond the amounts provided by the ordinary diabetic diet was not required These authors pointed out that perhaps severe vitamin deficiency does play a part in diabetic coma Certainly, this phase needs further clinical investigation

Bean and Spies⁶⁷ stressed that chronic diarrhea predisposes to the development of a deficiency syndrome by causing increased loss of, or

60 Brandenburg, K C Relief of Neuritis of Eighth Cranial Nerve with Vitamin B₁, *Arch Otolaryng* **31** 189-191 (Jan) 1940

61 Chesley, F F, Dunbar, J, and Crandall, L A, Jr The Vitamin B Complex and Its Constituents in Functional Digestive Disturbances, *Am J Digest Dis* **7** 24-27 (Jan) 1940

62 Moore, M T Treatment of Multiple Sclerosis with Nicotinic Acid and Vitamin B₁ Preliminary Report, *Arch Int Med* **65** 1-20 (Jan) 1940

63 Jankelson, I R Dysphagia Ascribed to Vitamin B Deficiency, *Am J Digest Dis* **7** 252-253 (June) 1940

64 Durand, J I, Spickard, V W, and Burgess, E Acrodynia Treated with Intramuscular Injections of Vitamin B₁, *J Pediat* **14** 74-78 (Jan) 1939 Williams, P, Shapiro, B G, and Bartelot, R Treatment of Acrodynia with Vitamin B₁ Given Parenterally, *Lancet* **1** 76 (Jan 13) 1940

65 Ochsner, A, and Smith, M C The Use of Vitamin B₁ for the Relief of Pain in Varicose Ulcers, *J A M A* **114** 947-948 (March 16) 1940

66 Owens, L B, Rockwern, S S, and Brown, E G Evaluation of Vitamin B Therapy for Diabetes, *Arch Int Med* **66** 679-687 (Sept) 1940

67 Bean, W B, and Spies, T D Vitamin Deficiencies in Diarrheal States, *J A M A* **115** 1078-1081 (Sept 28) 1940

decreased absorption of, vitamins. In addition to other vitamin supplements, these authors also suggested that 10 to 15 mg of thiamine hydrochloride be given parenterally each day to patients who have diarrhea. Field and his associates⁶⁸ pointed out that patients who received intensive alkaline therapy for peptic ulcer and achlorhydria had subnormal urinary excretions of thiamine. Therefore, more thiamine hydrochloride should be administered to patients with such conditions than to a normal person if a deficiency is to be prevented.

In a study of beriberi, Weiss⁶⁹ could not establish any significant difference between oriental and occidental beriberi. He stated that the cardiovascular manifestations of beriberi are related definitely to a deficiency of thiamine. He pointed out

The evidence now available on the causative relation between thiamin deficiency and cardiovascular dysfunction of beriberi is (a) thiamin deficiency in the diet, (b) decreased thiamin content in the urine, (c) disappearance of the disease after the administration of thiamin chloride, (d) induction of electrocardiographic changes in healthy men consuming a diet lacking only thiamin chloride, (e) induction in animals on a thiamin deficient diet of cardiac disturbances, including cardiac dilatation, electrocardiographic changes, congestive failure of the circulation and structural changes similar to or identical with those observed in man, and (f) disappearance of the experimentally induced cardiovascular dysfunction in animals after administration of thiamin chloride.

NICOTINIC ACID

Chemical and Physiologic Properties—As the authors of last year's review observed,⁷⁰ nicotinic acid bears a close relation to an enzyme system. Experimental studies seem to establish conclusively this relationship between nicotinic acid and the factor V (coenzymes 1 and 2 and possibly unknown related substances).⁷¹ Although the content of these compounds in the blood is not uniformly diminished in cases of pellagra in human beings (and hence is not of diagnostic or prognostic value), the administration of nicotinic acid has been shown to increase almost

68 Field, H., Jr., Robinson, W. D., and Melnick, D. The Destruction of Thiamin by Unacidified Bile and Pancreatic Juice. A Possible Explanation of the Cord Changes in Pernicious Anemia, *J. Clin. Investigation* **19** 791 (Sept.) 1940.

69 Weiss, S. Occidental Beriberi with Cardiovascular Manifestations. Its Relation to Thiamin Deficiency, *J. A. M. A.* **115** 832-839 (Sept. 7) 1940.

70 Wilder, R. M., Browne, H. C., and Butt, H. R. Diseases of Metabolism and Nutrition. Review of Certain Recent Contributions, *Arch. Int. Med.* **65** 390-460 (Feb.) 1940.

71 Axelrod, A. E., and Elvehjem, C. A. Effect of Nicotinic Acid Deficiency on the Cozymase Content of Tissues, *Nature, London* **143** 281-282 (Feb. 18) 1939. Kohn, H. I., Klein, J. R., and Dann, W. J. The V-Factor Content and Oxygen Consumption of Tissues of the Normal and Blacktongue Dog, *Biochem. J.* **33** 1432-1442 (Sept.) 1939.

invariably the level of this factor in the blood of both normal persons⁷² and patients who have pellagra. Although it is not known whether human organs undergo changes in the content of cozymase parallel with those observed in animal tissues, Elvehjem⁷³ stated that the rapid improvement produced in human beings and animals may be due to the rapid formation of cozymase. Kodicek⁷⁴ found little or no free nicotinic acid in living animal tissues and concluded that in autolysis of tissue this substance was set free from the coenzymes or from related compounds.

In contradiction to the previous finding of Vilter, Vilter and Spies, it was shown by Kohn and Klein⁷⁵ that erythrocytes of human blood can synthesize factor V from nicotinic acid in vitro.

Clinical investigations were carried out which demonstrated the role of nicotinic acid in carbohydrate metabolism with relation to diabetes,⁷⁶ in the administration of insulin⁷⁷ and in cerebral carbohydrate metabolism⁷⁸. The last factor was suggested as the possible basis for an explanation of the mental changes observed in persons with pellagra. Sydenstricker and his associates⁷⁶ observed 2 patients with complicated diabetes in whom the clinical signs of pellagra appeared if the carbo-

72 (a) Kohn, H. I. The Concentration of Coenzyme-Like Substance in Blood Following Administration of Nicotinic Acid to Normal Individuals and Pellagrins, *Biochem J* **32** 2075-2083, 1938. (b) Vilter, R. W., Vilter, S. P., and Spies, T. D. Relationship Between Nicotinic Acid and a Coohydrogenase (Cozymase), *J. A. M. A.* **112** 420-422 (Feb. 4) 1939. (c) Kohn, H. I., Bernheim, F., and Felsovanyi, A. V. The Blood V-Factor (Coenzyme) Level in Normal and Pathological Subjects, *J. Clin. Investigation* **18** 585-591 (Sept.) 1939. (d) Axelrod, A. E., Gordon, E. S., and Elvehjem, C. A. The Relationship of the Dietary Intake of Nicotinic Acid to the Coenzyme I Content of Blood, *Am. J. M. Sc.* **199** 697-705 (May) 1940. (e) Axelrod, A. E., Madden, R. J., and Elvehjem, C. A. The Effect of Nicotinic Acid Deficiency upon the Coenzyme I Content of Animal Tissues, *J. Biol. Chem.* **131** 85-93 (Nov.) 1939. (f) Vilter, S. P., Koch, M. B., and Spies, T. D. Coenzymes I and II in Human Blood, *J. Lab. & Clin. Med.* **26** 31-44 (Oct.) 1940.

73 Elvehjem, C. A. Relation of Nicotinic Acid to Pellagra, *Physiol. Rev.* **20** 249-271 (April) 1940.

74 Kodicek, E. Estimation of Nicotinic Acid in Animal Tissues, Blood and Certain Foodstuffs. II. Applications, *Biochem. J.* **34** 724-735 (May) 1940.

75 Kohn, H. I., and Klein, J. R. Synthesis of Factor V (Pyridine Nucleotides) from Nicotinic Acid in Vitro by Human Erythrocytes, *J. Biol. Chem.* **135** 685-689 (Sept.) 1940.

76 Sydenstricker, V. P., Geeslin, L. E., and Weaver, J. W. Avitaminosis Occurring in Diabetic Patients Under Insulin Therapy, *J. A. M. A.* **113** 2137-2138 (Dec. 9) 1939.

77 Burke, J. C., and McIntyre, A. R. Nicotinic Acid and the Vitamin B Complex in Insulin Tolerance, *J. Pharmacol. & Exper. Therap.* **67** 142-146 (Oct.) 1939.

78 Himwich, H. E., Spies, T. D., Fazekas, J. F., and Nesin, S. Cerebral Carbohydrate Metabolism During Deficiency of Various Members of the Vitamin B Complex, *Am. J. M. Sc.* **199** 849-853 (June) 1940.

hydrate in the diet and the dose of insulin were increased. These symptoms could be controlled with nicotinic acid, but recurred whenever the intake of carbohydrates and insulin was increased again. They noted similar occurrences in a case of diabetes and combined deficiency of nicotinic acid and riboflavin. They concluded from these observations that, since "co-enzymes I and II both contain nicotinic acid, it is quite possible that the great increase in dextrose metabolism might exhaust the body stores of this vitamin." This is in keeping with the finding by Vilter and associates^{72f} of a depleted coenzyme content in the blood of patients with diabetes who had ketosis. Sydenstricker and associates⁷⁶ further pointed out that the familiar glossitis and stomatitis occurring in persons with diabetes probably represent a vitamin deficiency rather than "lowered resistance" or a "toxic state."

Various methods have been suggested in the past for the chemical estimation of nicotinic acid, but the most satisfactory seems to be that which depends on the reaction with cyanogen bromide and aniline, which produces a yellow color. Numerous modifications of this procedure have been described during the past year⁷⁹. Although it had previously been reported⁸⁰ that normal persons excrete between 20 and 50 mg of nicotinic acid daily, more recent work has indicated that this value is probably too high and that the normal amount is between 3 and 12 mg daily. Only traces of nicotinic acid have been recovered from the urine

79 (a) Swaminathan, M. The Urinary Excretion of Nicotinic Acid, *Indian J. M. Research* **27** 417-428 (Oct.) 1939. (b) Bandier, E. Quantitative Estimation of Nicotinic Acid in Urine, *Biochem. J.* **33** 1787-1793 (Nov.) 1939. (c) Harris, L. J., and Raymond, W. D. Assessment of the Level of Nutrition. A Method for the Estimation of Nicotinic Acid in Urine, *ibid.* **33** 2037-2051 (Dec.) 1939. (d) Melnick, D., and Field, H., Jr. Determination of Nicotinic Acid in Biological Materials by Means of Photoelectric Colorimetry, *J. Biol. Chem.* **134** 1-16 (June) 1940. (e) Schindel, L. A Contribution to the Question of the Determination of Nicotinic Acid in Urine, *J. Lab. & Clin. Med.* **25** 515-516 (Feb.) 1940. (f) Melnick, D., and Field, H., Jr. Chemical Determination of Nicotinic Acid. Inhibitory Effect of Cyanogen Bromide upon the Aniline Side Reactions, *J. Biol. Chem.* **135** 53-58 (Aug.) 1940. (g) Najjar, V. A., and Wood, R. W. Presence of a Hitherto Unrecognized Nicotinic Acid Derivative in Human Urine, *Proc. Soc. Exper. Biol. & Med.* **44** 386-390 (June) 1940. (h) Rosenblum, L. A., and Jolliffe, N. Porphyrinuria in Pellagra, *Am. J. M. Sc.* **199** 853-858 (June) 1940. (i) Application to Urine of Bandier and Hald's Method for Determination of Nicotinic Acid, *J. Biol. Chem.* **134** 137-141 (June) 1940. (j) Melnick, D., Robinson, W. D., and Field, H., Jr. Influence of the Excretion of Other Pyridine Compounds upon the Interpretation of the Urinary Nicotinic Acid Values, *ibid.* **136** 131-144 (Oct.) 1940. (k) Urinary Excretion of Nicotinic Acid and Its Derivatives by Normal Individuals, *ibid.* **136** 145-156 (Oct.) 1940. (l) Factors Affecting the Concentration and Distribution of Nicotinic Acid in the Blood, *ibid.* **136** 157-166 (Oct.) 1940.

80 Vilter, S. P., Spies, T. D., and Mathews, A. P. A Method for the Determination of Nicotinic Acid, Nicotinamide, and Possibly Other Pyridine-Like Substances in Human Urine, *J. Biol. Chem.* **125** 85-98 (Sept.) 1938.

in the presence of a deficiency Najjar and Wood ^{79g} discovered a substance in human urine which they were unable to identify but which was increased by administration of nicotinic acid The presence of porphyrins in the urine was demonstrated to be of no value in the diagnosis of pellagra, but it probably reflects the presence of hepatic dysfunction ^{79h} Methods of biologic assay include the effect on the growth of bacteria and the growth response of dogs with blacktongue ⁸¹

Since the discovery of the antipellagra properties of nicotinic acid, various related pyridine derivatives have been subjected to investigation for evidence of similar properties From the work of Woolley and his associates ⁸² on dogs with blacktongue, it appeared that a rather specific structure was required to produce this activity They concluded that substances depend for their antiblacktongue activity on their ability to undergo oxidative or hydrolytic conversion to nicotinic acid or its amide in the body

In the activity of those compounds tried for the treatment of pellagra in human beings, there has been rather close correlation with the material in table 1 of Elvehjem ⁷³ The sodium and the ammonium salts of nicotinic acid were shown to possess activity ⁸³ and the diethyl amide (coramine) demonstrated some activity ⁸⁴ Pyrazine-2,3-dicarboxylic acid, pyrazine monocarboxylic acid, thiazolecarboxylic acid and quinolinic acid exhibited limited activity in the treatment both of the pellagra of human beings and of the blacktongue of dogs Spies and his associates ⁸⁵ reported that patients who had pellagra and were in a state of relapse were benefited by the administration of adenylc acid, but its use was not recommended because of the severe reactions which were produced

Clinical Use—Some doubt still exists as to whether nicotinic acid is the true pellagra-preventive factor If the rather pertinent suggestion

81 Elvehjem, C A , Waisman, H A , and Axelrod, A E Nicotinic Acid Its Distribution, Function and Relation to the Other Members of the B Complex, *J Nutrition* (supp) **17** 11, 1939

82 Woolley, D W , Strong, F M , Madden, R J , and Elvehjem, C A Anti-Black Tongue Activity of Various Pyridine Derivatives, *J Biol Chem* **124** 715-723 (Aug) 1938

83 Spies, T D , Bean, W B , and Stone, R E The Treatment of Subclinical and Classic Pellagra Use of Nicotinic Acid, Nicotinic Acid Amide and Sodium Nicotinate, with Special Reference to the Vasodilator Action and the Effect on Mental Symptoms, *J A M A* **111** 584-590 (Aug 13) 1938

84 Sydenstricker, V P , Schmidt, H L , Jr , Fulton, M C , New, J S , and Geeslin, L E Treatment of Pellagra with Nicotinic Acid Observations in Forty-Five Cases, *South M J* **31** 1155-1163 (Nov) 1938 Weinberg, M H Case of Subclinical Pellagra—Psychotic Type—Treated Successfully with Coramine (Nicotinic Acid), *Am J Psychiat* **96** 701-704 (Nov) 1939

85 Bills, C E , McDonald, F G , and Spies, T D Antipellagic Action of Pyrazine-2, 3-Dicarboxylic Acid and Pyrazine Monocarboxylic Acid, *South M J* **32** 793-795 (Aug) 1939 Spies, T D , Bean, W B , and Vilter, R W Adenylc Acid in Human Nutrition, *Ann Int Med* **13** 1616-1618 (March) 1940

of Sebiell and Butler⁸⁶ is followed and the diagnosis of pellagra is reserved for that syndrome which responds to the administration of nicotinic acid, this is then by definition the true pellagra-preventive factor. On the other hand, pellagra as encountered clinically is a disease of multiple deficiencies and must be treated as such. Taylor⁸⁷ made the interesting, though not new, suggestion that the cause of pellagra may be fourfold: (1) deficiency of the pellagra-preventive factor in the diet, (2) intrinsic deficiency in the gastric juice, (3) exposure to sunlight, and (4) an unidentified micro-organism. It should be remembered further that nicotinic acid alone will not prevent the recurrence of the cardinal symptoms of pellagra⁸⁸. The introduction of vitamin B₆ and pantothenic acid may prove to be of great importance in the treatment and control of pellagra.

Jolliffe and his associates⁸⁹ reported on the observation of 150 cases of a syndrome characterized by clouding of the consciousness, cogwheel rigidities and uncontrollable grasping and sucking reflexes, either with or without manifestations of any deficiency disease. By treatment with nicotinic acid and hydration, they were able to reduce the mortality rate of this syndrome from 89.4, 100 or 51.5 per cent to 13.6 per cent. They suggested that this syndrome represented an acute, complete lack of nicotinic acid, in contrast to pellagra, which they regarded as a chronic deficiency.

The well known effect of nicotinic acid in producing peripheral vasodilatation has led to an investigation of the possibility of its use in the treatment of peripheral vascular disease. In a study of 15 normal adults, Abramson and his associates⁹⁰ found that after oral administration of nicotinic acid the flow of blood to the forearm and hand was increased as much as two and a half times and the effect lasted as long as one hundred and sixty minutes, only a slight increase was observed in the flow to the lower extremities. Appreciable changes in blood pressure, pulse rate or cutaneous temperatures were not noted. They did not find significant differences in these effects when the intravenous

86 Sebiell, W. H., Jr., and Butler, R. E. Riboflavin Deficiency in Man (Ariboflavinosis), *Pub Health Rep* **54** 2121-2131 (Dec 1) 1939

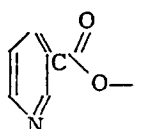
87 Taylor, F. R. The Etiology of Pellagra, *Am J Digest Dis* **6** 123-125 (April) 1939

88 Schmidt, H. L., Jr., and Sydenstricker, V. P. Nicotinic Acid in the Prevention of Pellagra. Preliminary Note, *J A M A* **110** 2065-2066 (June 18) 1938

89 Jolliffe, N., Bowman, K. M., Rosenblum, L. A., and Fein, H. P. Nicotinic Acid Deficiency in Encephalopathy, *J A M A* **114** 307-312 (Jan 27) 1940
Jolliffe, N. Effects of Vitamin Deficiency on Mental and Emotional Processes, *A Research Nerv & Ment Dis, Proc* (1938) **19** 114-153, 1939

90 Abramson, D. I., Katzenstein, K. H., and Senior, F. A. Effect of Nicotinic Acid on Peripheral Blood Flow in Man, *Am J M Sc* **200** 96-102 (July) 1940

rather than the oral route of administration was used. Estimations of cutaneous temperatures by Bean and Spies⁹¹ revealed that only those

compounds containing the radical  produced vasodilatation

and that related pellagra-preventive substances not containing this radical did not have a similar effect.⁹² They discovered that the administration of aminoacetic acid will prevent the vasodilatation, probably through conversion of nicotinic acid to nicotinuric acid. Others⁹³ observed the failure of nicotinic acid amide to cause flushing of patients. Although they observed an increase in cutaneous temperatures up to 1.5 degrees C (2.7 degrees F), Bean and Spies⁹¹ concluded that nicotinic acid will not prove to be of much value in the treatment of peripheral vascular disorders, indeed, they warned that its use may be dangerous.

Other conditions for which treatment with nicotinic acid has been suggested include otosclerosis,⁹⁴ Vincent's disease,⁹⁵ acne vulgaris,⁹⁶ infected scabies,⁹⁷ cyanosis resulting from the use of sulfanilamide⁹⁸ and xerostomia.⁹⁹ Frostig and Spies⁹² reported the successful treatment of a type of psychoneurosis which they considered as resulting from a specific deficiency of nicotinic acid.

Calder and Kerby¹⁰⁰ observed that the administration of nicotinic acid in vitro to patients who had brucellosis reduced the clotting time of the blood to normal and effected normal retraction of the clot. They

91 Bean, W. B., and Spies, T. D. A Study of the Effects of Nicotinic Acid and Related Pyridine and Pyrazine Compounds on the Temperature of the Skin of Human Beings, *Am Heart J* **20** 62-76 (July) 1940.

92 Frostig, J. P., and Spies, T. D. The Initial Nervous Syndrome of Pellagra and Associated Deficiency Diseases, *Am J M Sc* **199** 268-274 (Feb) 1940.

93 Field, H. J., and Robinson, W. D. The Absence of Reactions Following Therapeutic Doses of Nicotinic Acid Amide, *Am J M Sc* **199** 275-276 (Feb) 1940.

94 Selfridge, G. Nicotinic Acid in the Eighth Nerve. Preliminary Report, *Ann Otol, Rhin & Laryng* **48** 39-53 (March) 1939, The Eighth Nerve in Relation to Thiamin Chloride and Nicotinic Acid. A Comparative Study, *ibid* **48** 419-432 (June) 1939.

95 King, J. D. Vincent's Disease Treated with Nicotinic Acid, *Lancet* **2** 32-35 (July 13) 1940.

96 Lynch, F. W. Nicotinic Acid in the Treatment of Acne Vulgaris, *Arch Dermat & Syph* **42** 481-482 (Sept) 1940.

97 Goodall, J. W. D. Observations on the Use of Nicotinic Acid in the Treatment of Pellagra and Allied Conditions, *Indian M Gaz* **75** 147-153 (March) 1940.

98 Doughty, J. F. Sulfanilamide Cyanosis Relieved by Nicotinic Acid, *J A M A* **114** 756 (March 2) 1940.

99 Saphir, W. Xerostomia Successfully Treated with Nicotinic Acid, *Am J Digest Dis* **7** 298-299 (July) 1940.

100 Calder, R. M., and Kerby, G. P. The Effect of Nicotinic Acid on Blood Coagulation, *Am J M Sc* **200** 590-596 (Nov) 1940.

reported that administration of nicotinic acid to patients who had hemorrhagic tendencies (typhoid fever, hypoplastic anemia or acute catarrhal jaundice) seemed to bring about correction of this disorder. Effects were not noted when the blood of patients who had hemophilia was used. An explanation of the mechanism by which these changes may be produced was not offered.

The proper dose of nicotinic acid has not yet been properly determined. Apparently, the drug is relatively nontoxic and the unpleasant flushing effect would seem to be without harm. Nicotinic acid amide does not produce this flushing.¹⁰¹

RIBOFLAVIN

Chemical and Physiologic Properties—Studies of distribution of riboflavin reveal that the liver and kidneys of swine, cattle, lambs and calves contain comparatively large amounts of riboflavin and that the muscular tissues of these animals contain less riboflavin than do the glandular tissues. Riboflavin was not lost from these tissues by the ordinary household method of stewing, but an appreciable amount was lost when samples were roasted or fried.¹⁰² It has been known for several years that tubercle bacilli contain a yellow pigment (phthiocol 1 [2-methyl-3-hydroxy-1, 4-naphthoquinone]), which recently has been shown to possess marked antihemorrhagic activity, similar to that of vitamin K. Street and Reeves¹⁰³ demonstrated more recently that a fluorescent yellow pigment in the tubercle bacillus apparently is identical with riboflavin.

During the last year several methods for determining the riboflavin content of foodstuffs¹⁰⁴ and the urinary excretion of riboflavin¹⁰⁵ were reported, but it is believed by most investigators that these methods can be improved.

Clinical Deficiency—That a deficiency of riboflavin occurs among human beings was reported by Sebrell and Butler,¹⁰⁶ as cited in this

¹⁰¹ Frostig and Spies⁹² Saphir⁹⁹

¹⁰² Mickelsen, O., Waisman, H. A., and Elvehjem, C. A. The Distribution of Riboflavin in Meat and Meat Products, *J. Nutrition* **18** 517-526 (Nov.) 1939

¹⁰³ Street, H. R., and Reeves, R. E. Occurrence of Riboflavin in Tubercle Bacillus, *Proc. Soc. Exper. Biol. & Med.* **44** 641-644 (June) 1940

¹⁰⁴ Hodson, A. Z., and Norris, L. C. A Fluorometric Method for Determining the Riboflavin Content of Foodstuffs, *J. Biol. Chem.* **131** 621-630 (Dec.) 1939

¹⁰⁵ Ferrebee, J. W. The Urinary Excretion of Riboflavin. Fluorometric Methods for Its Estimation, *J. Clin. Investigation* **19** 251-256 (Jan.) 1940. Fraser, H. F., Topping, N. H., and Isbell, H. The Bacterial Assay of Riboflavin in the Urine and Tissues of Normal and Depleted Dogs and Rats, *Pub. Health Rep.* **55** 280-289 (Feb. 16) 1940

¹⁰⁶ Sebrell, W. H., and Butler, R. E. Riboflavin Deficiency in Man. A Preliminary Note, *Pub. Health Rep.* **53** 2282-2284 (Dec. 30) 1938

review last year. This original work of Sebrell and Butler has now been amply confirmed by several investigators,¹⁰⁷ and within the past year Sebrell and his co-workers¹⁰⁸ have reported other symptoms which often are present among persons who subsist on a diet deficient in riboflavin. In addition to cheilosis and seborrheic accumulations at the nasolabial fold, they described a specific type of glossitis which often can be recognized before other signs of deficiency of riboflavin are present. The tongue is clean, the papillae are flat rather than atrophic, and the color is definitely purplish red or magenta, as compared with the scarlet-red tongue so often seen in patients with deficiency of nicotinic acid. These investigators pointed out that this type of glossitis often develops in patients with pellagra after the red and atrophic tongue has become normal in appearance from treatment with nicotinic acid while the diet has remained deficient in riboflavin. In addition to this newly observed characteristic of deficiency of riboflavin, the authors also described certain ocular changes which nearly always are present in such a deficiency. These ocular changes can be seen easily with a slit lamp. The earliest lesion is proliferation and engorgement of the limbic plexus, which progresses to superficial vascularization of the cornea and the production of interstitial keratitis. Photophobia, congestion of the sclera, vascularization and abnormal pigmentation of the iris, dimness of vision and actual impairment of visual acuity are relieved promptly, and at times dramatically, by the administration of riboflavin. From these studies the authors suggested that deficiency of riboflavin is perhaps one of the most prevalent forms of uncompensated avitaminosis. Similar results were obtained by Johnson and Eckardt¹⁰⁹.

It has also been reported¹¹⁰ that riboflavin is of value in the treatment of pemphigus.

107 Sydenstricker, V. P., Geeslin, L. E., Templeton, C. M., and Weaver, J. W. Riboflavin Deficiency in Human Subjects, *J. A. M. A.* **113** 1697-1700 (Nov 4) 1939. Jolliffe, N., Fein, H. D., and Rosenblum, L. A. Riboflavin Deficiency in Man, *New England J. Med.* **221** 921-926 (Dec 14) 1939. Shields, W. P. Riboflavin Deficiency. Report of a Case in a Child with Cure by Specific Treatment, *ibid.* **223** 215-216 (Aug 8) 1940.

108 Kruse, H. D., Sydenstricker, V. P., Sebrell, W. H., and Cleckley, H. M. Ocular Manifestations of Riboflavinosis, *Pub. Health Rep.* **55** 157-169 (Jan 26) 1940. Sydenstricker, V. P., Sebrell, W. H., Cleckley, H. M., and Kruse, H. D. The Ocular Manifestations of Ariboflavinosis. A Progress Note, *J. A. M. A.* **114** 2437-2445 (June 22) 1940.

109 Johnson, L. V., and Eckardt, R. E. Rosacea Keratitis and Conditions with Vascularization of Cornea Treated with Riboflavin, *Arch. Ophth.* **23** 899-907 (May) 1940.

110 Topping, M. C., and Knoefel, A. F. Use of Vitamin G in Pemphigus. Report of a Case of Pemphigus Vulgaris Treated Successfully with Riboflavin, *J. A. M. A.* **114** 2102 (May 25) 1940.

PYRIDOXINE (VITAMIN B₆)

Chemical and Physiologic Properties—It has been suggested¹¹¹ and accepted by many writers that pyridoxine be adopted as the chemical name for vitamin B₆ (2-methyl-3-hydroxy-4, 5-di-hydroxymethyl-pyridine). Like other members of the vitamin B complex, pyridoxine (administered both as the base and as the hydrochloride) was found experimentally to be relatively free from toxic action.¹¹² Excessively large doses (3 Gm per kilogram of body weight) produced convulsions and death in certain experimental animals, but long feeding of sublethal doses failed to produce symptoms of toxicity, which suggested that pyridoxine is either rapidly excreted or destroyed. Weigand and associates¹¹³ did not observe any ill effects on man after the oral or intravenous administration of pyridoxine hydrochloride in doses of 100 to 200 mg.

Colorimetric methods for measuring the urinary excretion of pyridoxine (vitamin B₆) were described.¹¹⁴ An average of 87 per cent of 50 mg of pyridoxine given intravenously was recovered within an hour from the urine of a group of healthy human beings, and 76 per cent of 100 mg administered orally was recovered from the urine within four hours.

Clinical Deficiency—It was reported last year¹¹⁵ that a syndrome characterized by "extreme nervousness, insomnia, irritability, abdominal pain, weakness and difficulty in walking" dramatically disappeared after intravenous administration of pyridoxine. This report was not confirmed by Kark and his associates,¹¹⁶ but since that time Spies and his co-workers¹¹⁷ have treated 20 patients with similar conditions and have obtained good results. In a further study of this problem, these authors

111 Gyorgy, P, and Eckardt, R E. Vitamin B₆ and Skin Lesions in Rats, *Nature*, London **144** 512 (Sept 16) 1939

112 Unna, K, and Antopol, W. Toxicity of Vitamin B₆, *Proc Soc Exper Biol & Med* **43** 116-118 (Jan) 1940

113 Weigand, C G, Eckler, C R, and Chen, K K. Action and Toxicity of Vitamin B₆ Hydrochloride, *Proc Soc Exper Biol & Med* **44** 147-151 (May) 1940

114 Scudi, J V, Koones, H F, and Keresztesy, J C. Urinary Excretion of Vitamin B₆ in the Rat, *Proc Soc Exper Biol & Med* **43** 118-122 (Jan) 1940
Scudi, J V, Unna, K, and Antopol, W. A Study of the Urinary Excretion of Vitamin B₆ by a Colorimetric Method, *J Biol Chem* **135** 371-376 (Sept) 1940

115 Spies, T D, Bean, W B, and Ashe, W F. A Note on the Use of Vitamin B₆ in Human Nutrition, *J A M A* **112** 2414-2415 (June 10) 1939

116 Kark, R, Lozner, E L, and Meiklejohn, A P. Negative Effect of Synthetic Vitamin B₆ Hydrochloride in Nutritional Deficiency in Man, *Proc Soc Exper Biol & Med* **43** 97-99 (Jan) 1940

117 Spies, T D, Ladisch, R K, and Bean, W B. Vitamin B₆ (Pyridoxin) Deficiency in Human Beings. Further Studies, with Special Emphasis on the Urinary Excretion of Pyridoxin, *J A M A* **115** 839-840 (Sept 7) 1940

observed that within an hour after intravenous injection of pyridoxine the average urinary excretion of this material by normal persons is 7.9 per cent and by patients with pellagra 8.6 per cent. Four patients of the group studied were suspected of having a deficiency of pyridoxine, and the lowest rate of excretion (averaging 0.2 per cent) of pyridoxine occurred among them. The absorption of pyridoxine apparently is dependent on the diet, as patients with a clinical deficiency disease who are placed on a diet deficient in pyridoxine are found to excrete none of the injected material. It was concluded from these results that pyridoxine is important to human nutrition, and this particular investigation gave strong support to the hypothesis, repeatedly mentioned by Spies, that a clinical deficiency disease occurs not as a single entity but as a complex syndrome.

Cheilosis is considered to be the result of a deficiency of riboflavin, but Smith and Martin¹¹⁸ reported that cheilosis can be treated successfully with synthetic pyridoxine hydrochloride. The authors reported several cases of typical cheilosis resulting from a deficiency of riboflavin in which a rather dramatic response occurred after administration of pyridoxine hydrochloride. The patient in 1 case which the authors reported had mild cheilosis associated with sprue. Although slight improvement of the lesions of the mouth occurred after administration of pyridoxine hydrochloride, complete healing did not result either from pyridoxine hydrochloride in doses of 1,000 mg. or from a combination of pyridoxine hydrochloride (300 mg.), riboflavin (140 mg.) and nicotinic acid (1,000 mg.). Finally the lesion healed after administration of 445 U. S. P. units of a concentrated liver extract given for one week. The authors gave three possible explanations for this peculiar observation: 1. A primary and specific deficiency of riboflavin is responsible for cheilosis, and pyridoxine acts only indirectly. 2. A primary and specific deficiency of pyridoxine is responsible for cheilosis, and riboflavin acts only indirectly. 3. Both riboflavin and pyridoxine are necessary to maintain the integrity of the lip at the mucocutaneous junction, and a deficiency of either will precipitate the lesion.

It has been well established that hypochromic anemia, which develops among dogs on a diet deficient in pyridoxine, is not relieved by the administration of iron.¹¹⁹ In this connection, Vilter and his associates¹²⁰

118 Smith, S. G., and Martin, D. W. Cheilosis Successfully Treated with Synthetic Vitamin B₆, *Proc Soc Exper Biol & Med* **43** 660-663 (April) 1940.

119 McKibbin, J. M., Madden, R. J., Black, S., and Elvehjem, C. A. The Importance of Vitamin B₆ and Factor W in the Nutrition of Dogs, *Am J Physiol* **128** 102-110 (Dec.) 1939.

120 Vilter, R. W., Schiro, H. S., and Spies, T. D. Effect of Synthetic Vitamin B₆ on the Haemopoietic System of Human Beings, *Nature*, London **145** 388 (March 9) 1940.

reported an interesting study on the effect of pyridoxine on the hemopoietic system of human beings. To 3 patients who had pellagra and macrocytic anemia and to 2 patients who had pernicious anemia, from 50 to 100 mg of crystalline pyridoxine in sterile physiologic solution of sodium chloride was administered intravenously each day for ten days. The patients experienced a sense of well-being and increased strength within forty-eight hours, and on the fifth, sixth, seventh and eighth days a slight but definite reticulocytosis appeared in each instance. The reticulocyte count did not exceed 5 per cent, but the leukocyte count, which was low in the 2 cases of pernicious anemia, increased during this period. The increase was principally in the polymorphonuclear leukocytes. In another experiment, 100 mg of pyridoxine was incubated with 100 cc of gastric juice from the stomachs of normal fasting human beings. This material was administered orally to 1 of the patients who had pernicious anemia, a response identical with that observed after the intravenous administration of pyridoxine was obtained. These findings suggested that pyridoxine administered in large amounts has a definite effect on the hemopoietic system of patients who are in a state of relapse as a result of macrocytic anemia associated with pellagra or pernicious anemia.

One of the most interesting reports of the possible use of pyridoxine in the treatment of human diseases was that of Jolliffe¹²¹ on its effect in cases of Parkinson's syndrome. This author selected 15 patients who had paralysis agitans and who were confined to bed or chair. To each of these patients 50 or 100 mg of pyridoxine hydrochloride was administered intravenously either every day or every other day. Of these 15 patients, 4 revealed subjective and definite objective improvement and 2 additional patients were subjectively improved. The conditions of these patients represented so-called arteriosclerotic, or idiopathic, and postencephalitic types of paralysis agitans. The beneficial effects of the administration of this compound were limited to lessening of rigidity and to an increase in strength. Tremor was not affected.

Other beneficial effects of pyridoxine on diseases of the nervous system have been observed by Vilter and his associates¹²². These investigators reported that partial remission of a severe polyneuritic syndrome caused by arsenic occurred after administration of pyridoxine in 1 case. The most spectacular remission in this particular case occurred when pyridoxine and alpha tocopherol were administered.

121 Jolliffe, N. Clinical Aspects of Vitamin B Deficiencies, *Minnesota Med* **23** 542-551 (Aug) 1940

122 Vilter, R. W., Aring, C. D., and Spies, T. D. A Case of Arsenic Peripheral Neuritis Treated with Synthetic Vitamin B₆ and Alpha-Tocopherol, *J. A. M. A.* **115** 209-211 (July 20) 1940

PANTOTHENIC ACID

It has been known for some time that a factor curative for chicken dermatitis is found in filtered extracts of liver or yeast. This factor was called "filtrate factor" or "chicken antidermatitis factor." Several investigators have shown that the growth of the chicken was proportional to the quality of filtrate factor in the diet, and others have demonstrated that nicotinic acid and various other vitamins did not cure chicken dermatitis. While this work was being carried out, Williams and his associates,¹²³ working along different lines, determined that distributed apparently through all living tissue was a substance which they called "pantothenic acid." Soon these authors established that pantothenic acid consisted of "beta-alanine and a hydroxy acid." In 1939 Woolley and his associates¹²⁴ and Jukes,¹²⁵ working independently, announced that the chick antidermatitis factor (filtrate factor of Jukes¹²⁵) appeared to be identical with the pantothenic acid described by Williams and his associates. Finally, in 1940, Williams and Major¹²⁶ announced the synthesis of pantothenic acid and described its formula. Pantothenic acid is a condensation product of beta alanine and alphahydroxybetabetadimethylgammabutyrolactone. This compound is destroyed by strong alkali and by dry heat, but it seems to be resistant to ordinary oxidizing and reducing agents.

Waisman and his associates¹²⁷ have reported that the liver and kidneys of various animals are the richest sources of pantothenic acid but that muscular tissues of cattle, lambs, swine and calves are poor sources. Ordinary stewing was found to decrease the potency of kidney, heart and spleen by a third, but the factor present in liver was not destroyed by frying. Jukes¹²⁸ found that extract of rice bran and bakers' yeast were excellent sources of this factor and that egg yolks, dried skimmed milk and alfalfa were also good sources. Carrots, onions

123 Rohman, E., Burget, G. E., and Williams, R. J. Pantothenic Acid Content of Animal Tissues, *Proc Soc Exper Biol & Med* **32** 473-474 (Dec.) 1934
Williams, R. J., Mosher, W. A., and Rohman, E. The Importance of "Pantothenic Acid" in Fermentation, Respiration and Glycogen Storage, *Biochem J* **30** 2036-2039, 1936

124 Woolley, D. W., Waisman, H. A., and Elvehjem, C. A. Studies on the Structure of the Chick Antidermatitis Factor, *J Biol Chem* **129** 673-679 (Aug.) 1939

125 Jukes, T. H. Pantothenic Acid and the Filtrate (Chick Anti-Dermatitis) Factor, *J Am Chem Soc* **61** 975-976 (April) 1939

126 Williams, R. J., and Major, R. T. The Structure of Pantothenic Acid, *Science* **91** 246 (March 8) 1940

127 Waisman, H. A., Mickelsen, O., and Elvehjem, C. A. The Distribution of the Chick Antidermatitis Factor (Pantothenic Acid) in Meats and Meat Products, *J Nutrition* **18** 247-256 (Sept.) 1939

128 Jukes, T. H. Further Observations on the Assay, Distribution and Properties of the Filtrate Factor, *J Biol Chem* **117** 11-20 (Jan.) 1937

and canned green peas were poor sources. Rolled oats, whole corn meal, canned Alaska salmon and fresh beef were found to be fair sources.

A variety of interesting occurrences take place among animals on a diet deficient in pantothenic acid. In the chick a condition of dermatitis rapidly results which is characterized by lesions on the eyelids, at the corners of the mouth and on the legs and feet. Some workers¹²⁹ observed that the spinal cord of animals deficient in pantothenic acid is affected and concluded that pantothenic acid is necessary to keep the normal structure of the spinal cord intact. When rats subsisted on a diet deficient in this compound cutaneous lesions and changes involving depigmentation of the fur of black rats and "rusting" of albino rats developed.¹³⁰

The only available reports on the effect of pantothenic acid and on its metabolism in human beings are those of Spies and his associates.¹³¹ These authors observed that doses of 100 mg of calcium or sodium pantothenate could be administered intravenously to human beings without any untoward reaction or changes in blood pressure, pulse rate, temperature or respiration. It was observed that the pantothenic acid content of the blood of 18 normal persons was between 1,900 and 3,200 micrograms per cubic centimeter and averaged 2,200 micrograms per cubic centimeter. It was observed further that after the intravenous injection of pantothenic acid, the content of the acid in the blood might increase to as much as 50 per cent above the preinjection level but that most of this increase was noted within the first three hours after injection. In each instance, however, the amount returned to its previous level within twenty-four hours. Analysis of specimens of urine likewise disclosed an increase in concentration of pantothenic acid after injection, the concentration returned to normal within twenty-four hours. In the blood of 28 patients who had pellagra, beriberi or a deficiency of riboflavin, the average level of pantothenic acid was only 5 to 900 micrograms per cubic centimeter. This was 23 to 50 per cent below the normal average.

After the intravenous injection of pantothenic acid, these authors also observed an increase of from 20 to 30 per cent in the level of riboflavin in the blood. Interestingly enough, the intravenous injection of 200 micrograms of riboflavin per kilogram of body weight was followed by an 80 per cent increase in the concentration of riboflavin in the blood.

129 Phillips, P. H., and Engel, R. W. Some Histopathologic Observations on Chicks Deficient in the Chick Antidermatitis Factor or Pantothenic Acid, *J Nutrition* **18** 227-232 (Sept.) 1939.

130 Gyorgy, P., Poling, C. E., and Subbarow, Y. Observations on the Factor Curative of Nutritional Achromatichia, *J Biol Chem* **132** 789-790 (Feb.) 1940.

131 Spies, T. D., Stanbery, S. R., Williams, R. J., Jukes, T. H., and Babcock, S. H. Pantothenic Acid in Human Nutrition, *J A M A* **115** 523-524 (Aug. 17) 1940. Stanbery, S. R., Snell, E. E., and Spies, T. D. Unpublished data.

and a 45 per cent increase in the level of pantothenic acid. These values remained elevated for three or four hours and in each instance returned to their former levels by the next day. These studies strongly indicate that perhaps pantothenic acid is essential to human nutrition and that its function is associated closely with that of riboflavin.

ASCORBIC ACID (VITAMIN C)

Chemical and Physiologic Properties—The possibility of ascorbic acid functioning in an oxidation-reduction enzyme system has been recognized for several years,¹³² but experimental proof of this action is still lacking. Investigations in this direction during the past year have failed to produce any concrete evidence that ascorbic acid acts as a respiratory enzyme or coenzyme. Schultze and his associates¹³³ demonstrated that ascorbic acid does not function as an agent in the transfer of hydrogen in a system containing nicotine hemochromogen, ascorbic acid, coenzyme, dextrose dehydrogenase and dextrose, further, cozymase did not reduce dehydroascorbic acid in vitro. Because of the circumstantial evidence for such a function of ascorbic acid, the problem remains an intriguing one and merits further investigation, as suggested in a recent editorial in *The Journal of the American Medical Association*.¹³⁴

It may well be that the efficacy of the vitamin as an antiscorbutic agent is related to a specific role in either oxidation-reduction reactions or to reactions that are responsible to a considerable degree for the transfer of hydrogen or electrons in the oxidation of metabolites.

The same editorial alluded to the work of Sealock and Silberstein,¹³⁵ who used guinea pigs that had alkaptonuria, and cited this work as "perhaps an in vivo example of a relation of ascorbic acid to oxidation processes." However, one of these investigators (Sealock) and other associates were unable to modify the excretion of homogentisic acid by the administration of 1 to 4 Gm of ascorbic acid daily to a patient with alkaptonuria.¹³⁶

132 King, C. G. Vitamin C, Ascorbic Acid, *Physiol Rev* **16** 238-262 (April) 1936

133 Schultze, M. O., Harrer, C. J., and King, C. G. Studies on the Possible Carrier Role of Ascorbic Acid in Animal Tissues, *J Biol Chem* **131** 5-12 (Nov) 1939

134 Possible Role of Ascorbic Acid in Animal Tissues, editorial, *J A M A* **114** 1668-1669 (April 27) 1940

135 Sealock, R. R., and Silberstein, H. E. The Excretion of Homogentisic Acid and Other Tyrosine Metabolites by the Vitamin C-Deficient Guinea Pig, *J Biol Chem* **135** 251-258 (Aug) 1940

136 Sealock, R. R., Galston, M., and Steele, J. M. Administration of Ascorbic Acid to an Alkaptonuric Patient, *Proc Soc Exper Biol & Med* **44** 580-583 (June) 1940

MacLean and associates¹³⁷ conducted an interesting experiment on guinea pigs that were on a diet deficient in ascorbic acid. They found that the principal lesion was related to the differentiation of the mesenchymal cells into osteoblasts and the stimulation of these osteoblasts to secrete bone matrix. They could not produce any evidence in support of the "jellation theory" of Wolbach and Howe. The formation of dentine in the teeth of guinea pigs attracted the attention of one group of investigators,¹³⁸ who found that in animals deficient in ascorbic acid the odontoblasts produced histologically normal dentine, but that the quantity produced was decreased in proportion to the inadequacy of vitamin C in the diet. They suggested the use of their procedures in the biologic assay of ascorbic acid.

The role of vitamin C in metabolism of calcium was studied by Lanford,¹³⁹ who observed that guinea pigs fed orange juice stored 8 per cent more calcium from the diet than did control animals. Others¹⁴⁰ were unable to note any effect of ascorbic acid on the serum calcium of guinea pigs, but Todhunter and Brewer^{140a} found that the phosphatase activity of the serum was markedly decreased in cases of severe scurvy. They concluded that this diminution was the result of the scurvy and not of the restricted intake of food. It had been suggested previously that ascorbic acid was a powerful activator of serum phosphatase.¹⁴¹ Chu and his associates,¹⁴² in a comprehensive study of the metabolism of calcium and phosphorus in 2 cases of mild scurvy and 1 case of osteomalacia, found that the bodily retention and serum content of these elements were unaffected by the administration of ascorbic acid.

137 MacLean, D. L., Sheppard, M., and McHenry, E. W. Tissue Changes in Ascorbic Acid Deficient Guinea-Pigs, *Brit J Exper Path* **20** 451-457 (Dec) 1939

138 Boyle, P. E., Bessey, O. A., and Howe, P. R. Rate of Dentin Formation in Incisor Teeth of Guinea Pigs on Normal and on Ascorbic Acid-Deficient Diets, *Arch Path* **30** 90-107 (July) 1940

139 Lanford, C. S. The Effect of Orange Juice on Calcium Assimilation, *J Biol Chem* **130** 87-95 (Sept) 1939

140 (a) Todhunter, E. N., and Brewer, W. The Ascorbic Acid, Phosphatase and Calcium Content of the Blood of Guinea Pigs with Varying Degrees of Scurvy, *Am J Physiol* **130** 310-318 (Aug) 1940. (b) Henry, K. M., and Kon, S. K. The Retention of Calcium by the Rat in the Presence and in the Absence of Vitamin C, *Biochem J* **33** 1652-1654 (Oct) 1939

141 Maddock, S., Thannhauser, S. J., Reichel, M., and Grattan, J. A New Conception of Serum Phosphatase. Review of Experimental Work, *New England J Med* **218** 166-169 (Jan 27) 1938

142 Chu, H. I., Liu, S. H., Ch'en, K. C., Yu, T. F., Hsu, H. C., and Cheng, T. Y. The Effect of Vitamin C on the Calcium, Phosphorus and Nitrogen Metabolism in Scurvy and Osteomalacia, *Chinese J Physiol* **15** 101-118 (Jan 30) 1940

Shepherd and his associates¹⁴³ noted some effect of ascorbic acid on the retention of calcium, phosphorus and nitrogen in children

That loss of resistance to infections was caused by deficiency of ascorbic acid has been postulated in the past, the experimental work has given rise to varying conclusions. During the last year, investigations of this problem in the field of animal experimentation have been rather meager. King and his associates¹⁴⁴ produced marked injury with diphtheria toxin to the odontoblasts and dentine in the teeth of guinea pigs and were able to prevent this by administration of ascorbic acid. Sigal¹⁴⁵ demonstrated the protective action of vitamin C against changes in the cells of circulating blood produced by diphtheria toxin. Torrance¹⁴⁶ found a significant reduction in the content of ascorbic acid in the skin of rabbits and guinea pigs at the site of injection of diphtheria toxin, but this reduction was no greater than that produced by thermal burns, he concluded that these changes were dependent on the inflammatory reaction and were not of a specific nature.

Murakami,¹⁴⁷ in a study of the hepatic function of guinea pigs deficient in ascorbic acid, demonstrated a reduction in the amount of bile secreted, in the pigment-excreting function (azorubin S test) and in the capacity to detoxify indole. All of these factors were restored to normal levels by administration of ascorbic acid.

Metabolism of Vitamin C—Farmer, Abt and Chinn¹⁴⁸ demonstrated rather conclusively that the absorption of ascorbic acid from the intestinal tract of healthy persons is nearly complete, as the amount excreted in

143 Shepherd, M. L., Macy, I., Hunscher, H. A., and Hummel, F. C. Synthesized, Processed, and Natural Sources of Vitamin C in the Mineral Metabolism of Normal Children, *J. Pediat.* **16** 704-716 (June) 1940.

144 King, C. G., Musulin, R. R., and Swanson, W. F. Effects of Vitamin C Intake upon the Degree of Tooth Injury Produced by Diphtheria Toxin, *Am. J. Pub. Health* **30** 1068-1072 (Sept.) 1940.

145 Sigal, A. Effects of Vitamin C Deficiency and Diphtheria Toxin on Cellular Blood Constituents of Guinea Pig, *Proc. Soc. Exper. Biol. & Med.* **42** 163-167 (Oct.) 1939.

146 Torrance, C. C. The Ascorbic Acid Concentration of Inflammatory Lesions of the Skin, *J. Infect. Dis.* **67** 53-58 (July-Aug.) 1940.

147 Murakami, O. The Influence of Ascorbic Acid upon the Liver Function and the Mutual Relation Between Vitamins B₁ and C. I. The Influence of Ascorbic Acid upon the Pigment-Excreting Function of the Liver, *Jap. J. Gastroenterol.* **11** 1-6 (July) 1939, II. The Influence of Ascorbic Acid upon the Sodium Santonin-Managing Function of the Liver, *ibid.* **11** 7-12 (July) 1939, III. The Influence of Ascorbic Acid upon the Indol-Detoxifying Function of the Liver, *ibid.* **11** 12-23 (July) 1939, IV. The Mutual Relationship Between Vitamins B₁ and C Regarding the Detoxifying Function of the Liver for Indol, *ibid.* **11** 24-30 (July) 1939.

148 Farmer, C. J., Abt, A. F., and Chinn, H. The Absorption of Vitamin C (*L*-Ascorbic Acid) from the Intestinal Tract, in Health and Disease, *Quart. Bull., Northwestern Univ. M. School* **14** 114-119, 1940.

the feces is usually less than 5 mg in twenty-four hours. From experiments with guinea pigs, it appeared that this absorption occurred through a process of osmosis and diffusion and that phosphorylation was not required. Although they failed to find any increased intestinal excretion in the presence of high levels of ascorbic acid in the blood plasma, they regarded the possibility of reexcretion into the intestinal tract as unlikely. In the presence of increased intestinal motility, however, Abt, Farmer and Topper¹⁴⁹ found as much as 52 mg of ascorbic acid in a twenty-four hour sample of feces, and they cautioned that the loss by such routes may be severe enough to deplete the ascorbic acid in the plasma. Wright and Ludden¹⁵⁰ found 380 mg of ascorbic acid in the stools in twenty-four hours in cases of chronic diarrhea. They devised a formula for determining deficiency of absorption, which obviates the necessity of determining the ascorbic acid in the stools.

Sherry and his co-workers,¹⁵¹ who performed clearance tests with ascorbic acid and creatinine on dogs, reaffirmed the opinion that ascorbic acid is excreted by glomerular filtration and active tubular reabsorption. This reabsorption mechanism appeared limited by a maximal rate, and if this rate was exceeded by the rate at which the vitamin was supplied by the glomerular filtrate the entire excess quantity was excreted in the urine. Although ascorbic acid is, in a general sense, a threshold substance, tubular reabsorption is never complete in human beings, if the level of ascorbic acid in the plasma is less than 1.5 mg per hundred cubic centimeters the clearance of ascorbic acid is constant and independent of the concentration in the plasma.¹⁵² Barbiturates and certain analgesic drugs,¹⁵³ the salicylate group in particular,¹⁵⁴ produce diuresis of ascorbic acid in animals. This observation is interpreted by some as evidence of increased endogenous formation of the vitamin in relation

149 Abt, A. F., Farmer, C. J., and Topper, Y. J. Influence of Catharsis and Diarrhea on Gastrointestinal Absorption of Ascorbic Acid in Infants, *Proc Soc Exper Biol & Med* **43** 24-26 (Jan) 1940

150 Wright, I., and Ludden, J. B. Treatment with Vitamin C (Cevitamic Acid-Ascorbic Acid) Method for Compensating for the Factor of Error Due to Renal Retention of Vitamin C Found in All Previous Saturation and Blood Tests, *M Clin North America* **24** 743-758 (May) 1940

151 Sherry, S., Friedman, G. J., Paley, K., Berkman, J., and Ralli, E. P. The Mechanism of the Excretion of Vitamin C by the Dog Kidney, *Am J Physiol* **130** 276-280 (Aug) 1940

152 Friedman, G. J., Sherry, S., and Ralli, E. P. The Mechanism of the Excretion of Vitamin C by the Human Kidney at Low and Normal Plasma Levels of Ascorbic Acid, *J Clin Investigation* **19** 685-689 (Sept) 1940

153 Longenecker, H. E., Fricke, H. H., and King, C. G. The Effect of Organic Compounds upon Vitamin C Synthesis in the Rat, *J Biol Chem* **135** 497-510 (Sept) 1940

154 Samuels, L. T., Ritz, N. D., and Poyet, E. B. The Effect of Drugs on Vitamin C Excretion, *J Pharmacol & Exper Therap* **68** 465-475 (April) 1940

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to the animals' processes of detoxification Ralli and Sherry¹⁵⁵ observed a decrease in both the concentration in plasma and the urinary excretion after injection of insulin into diabetic dogs They were able to overcome this effect by the intravenous administration of dextrose

Butler and Cushman¹⁵⁶ made an interesting and important contribution to the knowledge of the distribution of ascorbic acid in the blood They described procedures for the determination of the ascorbic acid content of erythrocytes, leukocytes, platelets and whole blood In the leukocytes they found an average value of 34 mg of ascorbic acid equivalents per hundred grams of the white layer of centrifuged blood of normal persons and complete absence of the vitamin in the blood of persons with scurvy These procedures may well prove to be a more accurate index of the vitamin C nutrition of the body than the determination of the vitamin C content of the plasma of fasting persons Evidence was presented¹⁵⁷ which indicated that ascorbic acid passes from the plasma into the erythrocytes, its ratio of distribution varying with the state of ascorbic acid nutrition

Methods Used in the Diagnosis of Deficiency—In a previous review¹⁵⁸ it was noted that the simplest procedure for determining the state of ascorbic acid nutrition was estimation of ascorbic acid in the plasma after fasting More recent evidence would indicate that this may not be an accurate index of the body's reserve of the vitamin Several investigators¹⁵⁹ who used this method with healthy persons often found values within the "scorbutic range", the plasma of many apparently healthy persons contained less than 0.1 mg per hundred cubic centimeters Snelling^{159a} expressed the belief that there was "no

155 Ralli, E. P., and Sherry, S. Effects of Insulin on Plasma Level and Excretion of Vitamin C, *Proc Soc Exper Biol & Med* **43** 669-672 (April) 1940

156 Butler, A. M., and Cushman, M. Distribution of Ascorbic Acid in the Blood and Its Nutritional Significance, *J Clin Investigation* **19** 459-467 (May) 1940

157 (a) Heinemann, M., and Hald, P. M. Factors That Influence the Passage of Ascorbic Acid from Serum to Cells in Human Blood, *J Clin Investigation* **19** 469-473 (May) 1940 (b) Butler and Cushman¹⁵⁶

158 Wilder, R. M., Rutledge, D. I., and Wilbur, D. L. Diseases of Metabolism and Nutrition. Review of Certain Recent Contributions, *Arch Int Med* **63** 356-427 (Feb) 1939

159 (a) Snelling, C. E. The Plasma Ascorbic Acid of Infants and Children, *J Pediat* **15** 824-830 (Dec) 1939 (b) Yu, T. F. Blood Vitamin C Content of Chinese in Peiping During the Winter of 1938 to 1939, *Chinese M J* **56** 334-344 (Oct) 1939 (c) Mindlin, R. L. Variations in the Concentration of Ascorbic Acid in the Plasma of the Newborn Infant, *J Pediat* **16** 275-284 (March) 1940 (d) Harris, L. J. Assessment of the Level of Nutrition. Tests for Vitamin C on Groups of Poorly Fed and Well-Fed School-Children, *Lancet* **2** 259-263 (Aug 31) 1940 (e) Minot, A. S., Dodd, K., Keller, M., and Frank, H. A Survey of the State of Nutrition with Respect to Vitamin C in a Southern Pediatric Clinic, *J Pediat* **16** 717-728 (June) 1940

justification in the use of this method for the diagnosis of scurvy." In large groups, there seemed to be a parallelism between the content of ascorbic acid in the plasma and the adequacy of the diet, but this was not necessarily true in individual cases.

Various methods which depend on the increased excretion on the elevated plasma levels following the administration of test doses of ascorbic acid have been described for the estimation of the state of ascorbic acid nutrition. Several authors¹⁶⁰ have concluded that these methods are superior to those which depend on fasting levels of plasma. The former may be criticized on the grounds that they reflect the body's saturation with ascorbic acid, which condition may not be entirely necessary to health. Ludden and Wright¹⁶¹ devised a rather ingenious formula for a simplified method of determining the twenty-four hour excretion of ascorbic acid in the presence of renal insufficiency.

On finding low urinary excretion of ascorbic acid and normal levels in the plasma in cases of Addison's disease, Jenovese, Osterberg and Ryneerson¹⁶² concluded that determination of the ascorbic acid in the plasma alone is not an accurate index of deficiency of ascorbic acid in such cases.

The measurement of capillary fragility¹⁶³ and intradermal dye tests¹⁶⁴ have been rather conclusively demonstrated to be of little value.

New procedures continue to appear for the chemical determination of ascorbic acid in biologic materials and body fluids,¹⁶⁵ as well as methods which obviate sources of error in these determinations.¹⁶⁶

160 Kajdi, L., Light, J., and Kajdi, C. A Test for the Determination of the Vitamin C Storage. *Vitamin C Index, J. Pediat* **15** 197-218 (Aug.) 1939. Richardson, J. E., and Mayfield, H. L. The Amount of Ascorbic Acid Excreted at Each Urination During Twenty-Four-Hour Periods, *Am. J. Physiol* **128** 583-587 (Feb.) 1940. Pemberton, J. A Rapid Method of Differentiating Children with Large or Small Reserves of Vitamin C, *Brit. M. J.* **2** 217-219 (Aug. 17) 1940.

161 Ludden, J. B., and Wright, I. Effect of Renal Retention of Vitamin C on Saturation Tests. A Formula for Compensation of This Factor of Error, *Arch. Int. Med.* **65** 151-162 (Jan.) 1940. Wright and Ludden¹⁵⁰.

162 Jenovese, J. F., Osterberg, A. E., and Ryneerson, E. H. Role of Vitamin C in Addison's Disease, *Proc. Soc. Exper. Biol. & Med.* **44** 335-339 (June) 1940.

163 Rapaport, H. G., Miller, S. H., and Sicular, A. Capillary Fragility and Ascorbic Acid Studies, *J. Pediat* **16** 624-626 (May) 1940.

164 Rapaport, H. G., and Miller, S. H. The Determination of Vitamin C in Children by Intradermal Injection, *J. Pediat* **16** 503-507 (Oct.) 1939. Bakhsh, I., Kochhar, B. D., and Malik, A. Q. The Evaluation of the Intradermal Dye Test for Vitamin C in Health and Disease, *Indian J. M. Research* **27** 695-703 (Jan.) 1940.

165 Woessner, W. W., Elvehjem, C. A., and Schuette, H. A. The Determination of Ascorbic Acid in Commercial Milks, *J. Nutrition* **18** 619-626 (Dec.) 1939. Odén, M. C-Vitaminstandard und C-Hypovitaminose. II. Bestimmung von Ascorbinsäure mittels der photoelektrischen Zelle, *Acta pædiat.* **26** 351-361, 1939.

Data on Clinical Use—The possibility that ascorbic acid may have a role in the healing of wounds after operations has attracted the attention of several investigators. Wolfer and Hoebel¹⁶⁷ presented an excellent historical summary of the healing of wounds in the presence of scurvy. The tendency to failure of healing under such a condition was observed by laymen two centuries ago. Among other things, Wolfer and Hoebel¹⁶⁷ reported that a postoperative decrease in the content of ascorbic acid in the blood occurred not infrequently. Various explanations were advanced, including (1) increased destruction of ascorbic acid, (2) increased utilization of ascorbic acid in healing, (3) increased storage of the vitamin and (4) abnormal function of the bowel. The long periods of intravenous therapy without intake of food by mouth which so commonly follow surgical procedures were mentioned by them as an important factor in this respect. They stated that many patients undergo operation who already have deficiency of ascorbic acid. They suggested that the following groups of patients should be investigated for the presence of such a condition: (1) those who are receiving a deficient diet, as ascertained from the history, (2) those who are receiving large doses of alkalis by mouth, (3) those who have obstructive lesions of the gastrointestinal tract, (4) those who have had long periods of vomiting (and they may well have added "or diarrhea"), and (5) those who have syphilis or are addicted to alcohol. They recommended that the patient who has deficiency of vitamin C be given 1 Gm of ascorbic acid daily for ten days before operation is attempted and that this dose be continued after operation until healing is complete. Several cases were reported in which treatment with ascorbic acid seemed to be effective in bringing about proper healing of surgical wounds. Particularly striking was that of 1 patient (case 3 in Wolfer's¹⁶⁸ report) in whom secondary closure of an eviscerated wound was followed by prompt healing after administration of ascorbic acid.

Woessner, W. W., Elvehjem, C. A., and Schuette, H. The Determination of Ascorbic Acid in Evaporated Milk, Powdered Milk and Powdered Milk Products. *J. Nutrition* **20** 327-338 (Oct 10) 1940. Bryan, A. H., Turner, D., Lotwin, G., and Huenermann, R. L. The Estimation of the Ascorbic Acid Content of the Diet. *J. Am. Dietet. A* **16** 891-897 (Nov) 1940. Henemann and Hald^{157a}

166 Greenberg, L. D., and Rinehart, J. F. The Stability of Ascorbic Acid in Blood. *J. Lab. & Clin. Med.* **25** 1288-1294 (Sept) 1940. Sherry, S., and Friedman, G. J. Recovery of Vitamin C from the Human Bladder. *Proc. Soc. Exper. Biol. & Med.* **42** 707-709 (Dec) 1939. Kassan, R. J., and Roe, J. H. The Preservation of Ascorbic Acid in Drawn Samples of Blood. *J. Biol. Chem.* **133** 579-584 (April) 1940.

167 Wolfer, J. A., and Hoebel, F. C. The Significance of Cevitamic Acid Deficiency in Surgical Patients. *Surg., Gynec. & Obst.* **69** 745-755 (Dec) 1939.

168 Wolfer, J. A. The Surgical Aspect of Vitamin-C Deficiency. *S. Clin. North America* **20** 225-240 (Feb) 1940. Wolfer and Hoebel¹⁶⁷

Although it seems logical that dietary deficiency might be a factor in the failure of wounds to heal, Crandon and Lund¹⁶⁹ conducted an unusual experiment which tended to indicate that ascorbic acid avitaminosis may not be specific in this respect. By dietary measures they obtained total depletion of the ascorbic acid reserves in a healthy man as evidenced by complete absence of ascorbic acid in the blood plasma, leukocytes and platelets. Although they were unable to recover any ascorbic acid from a specimen of muscle removed for biopsy from the region of a wound produced for purposes of study, this wound healed as rapidly and firmly as that of a control subject, microscopic examination of the specimen failed to reveal any lack of intercellular substance. In a more recent report¹⁷⁰ of observations on this same person, clinical evidence of scurvy was noted after the diet had been completely lacking in ascorbic acid for one hundred and thirty-two days. When the blood levels of ascorbic acid had been zero for one hundred and forty-one days, another wound was made, definite failure of healing occurred, and the tissues revealed lack of intercellular substance and of formation of capillaries. The administration of ascorbic acid brought about good healing, and considerable intercellular substance appeared within ten days. From these observations it would appear that present methods of estimating the reserve of ascorbic acid are relatively crude.

In 1939, Holmes and associates¹⁷¹ produced evidence that ascorbic acid was effective in the treatment and prevention of lead poisoning. Pillemer and his associates¹⁷² were unable to substantiate this observation in experiments on guinea pigs and concluded that although treatment with this substance had some effect in the prevention of neuroplumbism, it was completely ineffective as compared with treatment by removal from exposure. Dannenberg and his co-workers¹⁷³ found ascorbic acid to be valueless as a therapeutic agent in a case of lead poisoning.

Farmer, Abt and Aron¹⁷⁴ demonstrated that the administration of arsenic and iron to human beings caused a marked decrease in the

169 Crandon, J. H., and Lund, C. C. Vitamin C Deficiency in an Otherwise Normal Adult, *New England J. Med.* **222** 748-752 (May 2) 1940.

170 Crandon, J. H., Lund, C. C., and Dill, D. B. Experimental Human Scurvy, *New England J. Med.* **223** 353 (Sept. 5) 1940. Experimental Human Scurvy, editorial, *J. A. M. A.* **115** 1637-1638 (Nov. 9) 1940.

171 Holmes, H. N., Campbell, K., and Amberg, E. J. The Effect of Vitamin C on Lead Poisoning, *J. Lab. & Clin. Med.* **24** 1119-1127 (Aug.) 1939.

172 Pillemer, L., Seifter, J., Kuehn, A. O., and Ecker, E. E. Vitamin C in Chronic Lead Poisoning. An Experimental Study, *Am. J. M. Sc.* **200** 322-327 (Sept.) 1940.

173 Dannenberg, A. M., Wideman, A. H., and Friedman, P. S. Ascorbic Acid in the Treatment of Chronic Lead Poisoning. Report of a Case of Clinical Failure, *J. A. M. A.* **114** 1439-1440 (April 13) 1940.

174 Farmer, C. J., Abt, A. F., and Aron, H. C. S. Influence of Arsenicals, Bismuth and Iron on the Plasma Ascorbic Acid Level, *Proc. Soc. Exper. Biol. & Med.* **44** 495-499 (June) 1940.

amount of ascorbic acid in the plasma, whereas bismuth did not exert this effect. Of importance may be the observation that the administration of suitable doses of ascorbic acid to persons sensitive to arsenic permitted the resumption of treatment.

Further studies have continued to appear on the relation of deficiency of ascorbic acid to nutritional anemia, and the results have been conflicting. Aion¹⁷⁵ produced anemia in guinea pigs with diets deficient in ascorbic acid, this anemia was unaffected by administration of iron but responded to ascorbic acid. Lozner¹⁷⁶ demonstrated normal regeneration of hemoglobin in patients whose plasma did not contain any ascorbic acid.

Additional investigation of ascorbic acid nutrition in various infectious processes has added little to knowledge of this relation¹⁷⁷. Among the conditions studied were pneumonia,^{177c} rheumatoid arthritis¹⁷⁸ and pulmonary tuberculosis¹⁷⁹. The general consensus was that the diminished quantity of ascorbic acid in the plasma, so frequently encountered in febrile and in chronic infectious conditions, is nonspecific and is dependent rather on an increased utilization or a general state of malnutrition.

Merritt and Foster¹⁸⁰ were unable to find any deviations from normal values in the content of ascorbic acid in the blood of patients who had epilepsy, nor did they observe any changes among those patients who were treated with dilantin sodium and exhibited hypertrophic gingivitis. They concluded that this condition is not due to a deficiency of ascorbic acid, as suggested by Kimball¹⁸¹.

175 Aron, H. C. S. The Relation of Vitamin C Deficiency to Nutritional Anemia, *J. Nutrition* **18** 375-383 (Oct.) 1939.

176 Lozner, E. L. Studies on Hemoglobin Regeneration in Patients with Vitamin C Deficiency, *J. Clin. Investigation* **19** 787 (Sept.) 1940.

177 (a) Flexner, J., Chassin, M., and Wright, I. S. Studies on Herpes Simplex Encephalitis in Rabbits. I. The Therapeutic Effect of Vitamin C, Sulphanilamide and Pitressin, *J. Infect. Dis.* **66** 30-32 (Jan.-Feb.) 1940. (b) Abbasy, M. A. On the Relation Between Vitamin C and Infection, *J. Egyptian M. A.* **23** 87-105 (Feb.) 1940. (c) Gortz, G. Investigation of the Ascorbic Acid Excretion in the Urine of Healthy and Febrile Children, *Acta pædiat.* **27** 429-436, 1940.

178 Jacques, R. H. Relation Between Reduced Ascorbic-Acid Levels of the Blood Plasma and Rheumatoid Arthritis, *J. Bone & Joint Surg.* **22** 324-326 (April) 1940. Hall, M. G., Darling, R. C., and Taylor, F. H. L. The Vitamin C Requirement in Rheumatoid Arthritis, *Ann. Int. Med.* **13** 415-423 (Sept.) 1939.

179 Erwin, G. S., Wright, R., and Doherty, C. J. Hypovitaminosis-C and Pulmonary Tuberculosis, *Brit. M. J.* **1** 688-689 (April 27) 1940. Osborn, T. W. B., and Gear, J. H. S. Possible Relation Between Ability to Synthesize Vitamin C and Reaction to Tubercle Bacillus, *Nature, London* **145** 974 (June 22) 1940.

180 Merritt, H. H., and Foster, A. Vitamin C in Epilepsy. Dilantin Sodium Not a Cause of Vitamin C Deficiency, *Am. J. M. Sc.* **200** 541-544 (Oct.) 1940.

181 Kimball, O. P. The Treatment of Epilepsy with Sodium Diphenyl Hydantoinate, *J. A. M. A.* **112** 1244-1245 (April 1) 1939.

Human Requirements—The exact requirement of ascorbic acid in the diet of healthy persons is still unsettled. Most investigations indicated that the maximal intake necessary to produce saturation of the tissues is approximately 100 mg each day, or 1.5 to 1.7 mg per kilogram of body weight¹⁸². From the point of view of simple maintenance of good health, Fox and his associates¹⁸³ conducted an interesting experiment among mine workers. After supplementing the routine diet of these workers (which contained 12 to 25 mg of ascorbic acid daily) with 40 mg of ascorbic acid daily, they were unable to note any effect on changes in weight, physical efficiency or resistance to infectious or dental diseases.

Some speculation has arisen concerning the relative merits of the synthetic and the natural sources of ascorbic acid. Shepherd and her associates¹⁴³ found better retention of calcium, phosphorus and nitrogen during the use of ascorbic acid from natural sources, and Todhunter and associates¹⁸⁴ observed that ascorbic acid from natural sources was better than the synthetic product in prevention of hemorrhages in scorbutic guinea pigs. Variations¹⁸⁵ in blood plasma levels during the use of ascorbic acid from these different sources were not noted. It has been suggested that the juice of oranges and of lemons may contain an added antiscorbutic agent. Detrick and associates¹⁸⁶ did not find any evidence of this factor in citrin. In any event, these experiments seem to bear out the thesis that ascorbic acid from natural sources should be used whenever possible.

182 Chen, K. C., Yu, T. F., Liu, S. H., and Chu, H. I. Studies on the Vitamin C Requirement of Chinese Patients with Scurvy, *Chinese J. Physiol.* **15** 119-142 (April 30) 1940. Todhunter, E. N., and Robbins, R. C. Observations on the Amount of Ascorbic Acid Required to Maintain Tissue Saturation in Normal Adults, *J. Nutrition* **19** 263-270 (March) 1940. Ralli, E. P., Friedman, G. J., and Sherry, S. The Vitamin C Requirement of Man Estimated After Prolonged Studies of the Plasma Concentration and Daily Excretion of Vitamin C in Three Adults on Controlled Diets, *J. Clin. Investigation* **18** 705-714 (Nov.) 1939.

183 Fox, F. W., Dangerfield, L. F., Gottlich, S. F., and Jokl, E. Vitamin C Requirements of Native Mine Labourers. An Experimental Study, *Brit. M. J.* **2** 143-147 (Aug. 3) 1940.

184 Todhunter, E. N., Robbins, R. C., Ivey, G., and Brewer, W. A Comparison of the Utilization by Guinea Pigs of Equivalent Amounts of Ascorbic Acid (Vitamin C) in Lemon Juice and in the Crystalline Form, *J. Nutrition* **19** 113-120 (Feb.) 1940.

185 Todhunter, E. N., and Fatzer, A. S. A Comparison of the Utilization by College Women of Equivalent Amounts of Ascorbic Acid (Vitamin C) in Red Raspberries and in Crystalline Form, *J. Nutrition* **19** 121-130 (Feb.) 1940. Todhunter, Robbins, Ivey and Brewer¹⁸⁴.

186 Detrick, L. E., Dunn, M. S., McNamara, W. L., and Hubbard, M. E. Vitamin C Studies. I. The Effect of Vitamin P (Citrin) on Vitamin C Deficient Guinea Pigs, *J. Lab. & Clin. Med.* **25** 684-687 (April) 1940.

VITAMIN D

Chemical and Physiologic Properties—Liu and his associates¹⁸⁷ reported some interesting observations on the function of vitamin D in relation to the body's metabolism of calcium and phosphorus. They demonstrated that in cases of osteomalacia the absence of vitamin D interfered with the intestinal absorption of calcium and led to loss of this mineral. In carefully conducted studies, they found that the first sign of deficiency of vitamin D was the disappearance of calcium from the urine, which they interpreted as an attempt by the body to conserve this mineral. An increase of calcium in the stool followed, the quantity increased progressively with the deficiency until a negative calcium balance existed. The changes in metabolism of phosphorus differed only in that the urinary excretion of phosphorus increased. By adding as little vitamin D as that contained in one to two eggs to the diet each day, they were able to reverse these changes, and they observed that the effect of even these small doses was prolonged over many days. The metabolism of calcium and of phosphorus of nursing infants closely paralleled the aforementioned changes and was dependent on the content of vitamin D in the diet of the mother. Smith and Spector¹⁸⁸ presented additional evidence of the function of vitamin D in the absorption of calcium, since they were able to show that the addition of liquid petrolatum to the diet of rats interfered with the healing of rickets by ultraviolet irradiation. Cohn and Greenberg,¹⁸⁹ in studying the metabolism of radioactive phosphorus in rachitic rats, found the intestinal absorption of this element little increased by vitamin D, but did observe that the vitamin increased the absorption of inorganic phosphorus by bone from 25 to 50 per cent. Reasoning indirectly, they suggested that vitamin D may exert its action through the conversion of organic to inorganic phosphorus in the bone.

187 Liu, S. H. The Role of Vitamin D in the Calcium Metabolism in Osteomalacia, *Chinese M. J.* **57** 101-118 (Feb.) 1940. Liu, S. H., Chu, H. I., Su, C. C., Yu, T. F., and Cheng, T. Y. Calcium Phosphorus Metabolism in Osteomalacia. IX. Metabolic Behavior in Infants Fed on Breast Milk from Mothers Showing Various States of Vitamin D Nutrition, *J. Clin. Investigation* **19** 327-347 (March) 1940. Chu, H. I., Liu, S. H., Yu, T. F., Hsu, H. C., Cheng, T. Y., and Chao, H. C. Calcium and Phosphorus Metabolism in Osteomalacia. X. Further Studies on Vitamin D Action, Early Signs of Depletion and Effect of Minimal Doses, *ibid.* **19** 349-363 (March) 1940.

188 Smith, M. C., and Spector, H. Further Evidence of the Mode of Action of Vitamin D, *J. Nutrition* **20** 197-202 (Sept. 10) 1940.

189 Cohn, W. E., and Greenberg, D. M. Studies in Mineral Metabolism with the Aid of Artificial Radioactive Isotopes. III. The Influence of Vitamin D on the Phosphorus Metabolism of Rachitic Rats, *J. Biol. Chem.* **130** 625-634 (Oct.) 1939.

Sobel and his associates¹⁹⁰ made the interesting observation that in rats lead seemed to be deposited in the bones in a manner similar to that of calcium, and that lead, phosphorus and vitamin D formed a system for deposition of lead which appeared to be analogous to that for calcification. They demonstrated also that administration of vitamin D had the same effect on the content of lead in the blood as did the administration of calcium.

Lichtenstein¹⁹¹ demonstrated definite bactericidal power in the cod liver oil used for dressings and proved that this was closely related to its content of peroxides.

Successful synthesis of compounds related to the antirachitic vitamins was reported,¹⁹² and it is hoped that a suitable product will soon be available. New methods for the determination of vitamin D activity of foods and biologic materials appeared.¹⁹³ Warkany and Mabon,^{193d} who used a method of biologic assay employing rachitic rats, found the serum of normal persons to contain between 66 and 165 U. S. P. units of vitamin D per hundred cubic centimeters of blood.

Treatment of Rickets—Park¹⁹⁴ presented a complete review of the treatment of rickets and infantile tetany with vitamin D. For preventive measures he emphasized the importance of commencing early and reaching the full dose "certainly by the end of the second month" of life. He warned that in the active treatment of rickets milk containing vitamin D

190 Sobel, A. E., Yuska, H., Peters, D. D., and Kramer, B. The Biochemical Behavior of Lead. I. Influence of Calcium, Phosphorus and Vitamin D on Lead in Blood and Bone, *J. Biol. Chem.* **132** 239-265 (Jan.) 1940.

191 Lichtenstein, M. Cod-Liver-Oil Dressings. Their Mode of Action, *Lancet* **2** 1023-1026 (Nov. 11) 1939.

192 Milas, N. A., and Alderson, W. L., Jr. Studies in the Synthesis of the Anti-Rachitic Vitamins. I. The Synthesis of 3-[2'-Methylenecyclohexylidene-1']-propene-1, *J. Am. Chem. Soc.* **61** 2534-2537 (Sept.) 1939. Aldersley, J. B., Burkhardt, G. N., Gillam, A. E., and Hindley, N. C. The Synthesis of Compounds Related to the Antirachitic Vitamins. Part II, *J. Chem. Soc. London*, January 1940, pp. 10-16.

193 (a) Westerlung, A. A Biological Estimation of Vitamin D in Oils, *Upsala Lakaref. förh.* **45** 33-45, 1939. (b) Coward, K. H., and Kassner, E. W. The Determination of Vitamin D in Food Substances Containing Phosphorus, *Biochem. J.* **34** 538-541 (April) 1940. (c) Russell, W. C. Report on Vitamin D. Feeding of Non-Vitamin D Skim or Whole Milk with the Reference to Cod Liver Oil, *J. A. Off. Agric. Chem.* **23** 341-345 (May) 1940. (d) Warkany, J., and Mabon, H. E. Estimation of Vitamin D in Blood Serum. II. Level of Vitamin D in Human Blood Serum, *Am. J. Dis. Child.* **60** 606-614 (Sept.) 1940. (e) McChesney, E. W., and Homburger, E. A Modification of the Line Test Applicable to Chicken Vitamin D Assay, *J. Nutrition* **20** 339-349 (Oct. 10) 1940. (f) Nield, C. H., Russell, W. C., and Zimmerli, A. The Spectrophotometric Determination of Vitamins D₂ and D₃, *J. Biol. Chem.* **136** 73-79 (Oct.) 1940.

194 Park, E. A. The Therapy of Rickets, *J. A. M. A.* **115** 370-379 (Aug. 3) 1940.

did not exhibit sufficient activity to end the disease abruptly, he recommended the use of the various fish oil preparations in doses sufficient to furnish 1,000 U S P units of vitamin D daily, or even 10,000 to 20,000 units to premature infants. Attention was called to the essential role of calcium in the treatment of infantile tetany. Park¹⁹⁴ reasoned properly that the use of vitamin D alone in this condition was irrational. He included a comprehensive discussion of the use of sunlight and ultraviolet irradiation, the treatment of refractory rickets and the signs of toxicity from vitamin D therapy, a summary of the various sources of vitamin D and the relative costs of these different preparations completed an excellent presentation of this subject, which is highly recommended as a "must read" article to any physician who treats children in his practice.

Since the elaboration of *Vitaminstoss* (crystalline vitamin D₂) therapy by Braulke¹⁹⁵ in 1937, the great bulk of antirachitic investigation has been in this direction. Parenteral¹⁹⁶ administration of 500,000 to 1,000,000 U S P units of vitamin D to children who had rickets (including premature infants) was followed by uniformly rapid healing and complete absence of clinical evidence of toxicity. This method seems to have been given a clinical trial sufficiently thorough to establish it as a standard procedure. Vollmer^{196c} demonstrated more rapid healing in rachitic rabbits by administering crystalline vitamin D dissolved in ether and oil (0.4 cc of ether and 0.6 cc of peanut oil) than by employing only oil as the solvent. Zelson^{196d} proposed a plan (suggested by Vollmer) for the prevention of rickets by parenteral vitamin D "shock prophylaxis," which appears to possess many advantages over the present methods.

The relative antirachitic properties of vitamins D₂ and D₃ has received some attention, to the ultimate conclusion that no significant clinically effective difference exists between the two preparations.¹⁹⁷

195 Braulke, H. Die Indikationen der Rachitisbehandlung mit einmaliger Dosis von Vitamin D₂ (Vitaminstoss), *Ztschr f Kinderh* **59** 18-31, 1937, abstracted, *Am J Dis Child* **56** 643-644 (Sept) 1938.

196 (a) Gunnarson, S. Treatment of Rickets with a Single Massive Dose of Vitamin D₂, *Acta pædiat* **25** 69-81, 1939. (b) Stiom, J. The Treatment of Spasmophilia with a Single Massive Dose of Vitamin D₂, *ibid* **25** 251-265, 1939. (c) Vollmer, H. Treatment of Rickets and Tetany by Parenteral Administration of One Massive Dose of Vitamin D, *J Pediat* **16** 419-432 (April) 1940. (d) Zelson, C. Prevention of Rickets in Premature Infants with Parenteral Administration of Single Massive Doses of Vitamin D, *ibid* **17** 73-78 (July) 1940.

197 Morris, N., and Stevenson, M. M. Vitamins D₂ and D₃ in Infantile Rickets. A Comparison of Their Therapeutic Efficiency, *Lancet* **2** 876-879 (Oct 21) 1939. Himsworth, H. P., and Maizels, M. Vitamins D₂ and D₃ and A. T. 10 in Congenital Thyroid and Parathyroid Deficiency, *ibid* **1** 959-960 (May 25) 1940. Wilson, D. C. Potency of Vitamins D₂ and D₃ in Osteomalacia and Late Rickets, *ibid* **1** 961-962 (May 25) 1940. Park¹⁹⁴

As Park¹⁹⁴ pointed out, "One need not fear that the dosage of vitamin D will be toxic unless renal insufficiency exists or unless the dosage is extremely large." This statement seems to be well corroborated by observations on clinical "shock therapy,"¹⁹⁶ and animal intoxication has, with 1 exception,¹⁹⁸ been produced only by doses many times larger than those used clinically.¹⁹⁹ Vollmer^{190c} demonstrated the presence of toxic by-products in irradiated ergosterol and suggested that the crystalline vitamins may be more safely employed if large doses are given. It was his opinion that an infant who has rickets possesses a definitely greater tolerance for vitamin D than does a nonrachitic adult.

Treatment of Other Conditions—Knapp²⁰⁰ offered experimental evidence to indicate that vitamin D is a possible factor in progressive myopia. He was able to reduce myopia or check its progression in two thirds of his patients. Reports of the use of vitamin D in various diseases of the skin²⁰¹ are fragmentary and offer little of value.

Poer²⁰² treated 11 patients who had postoperative hypoparathyroid tetany and expressed the opinion that over a prolonged period vitamin D₂ and dihydrotachysterol are more effective than parathyroid extract.

VITAMIN E

Chemical and Physiologic Properties—Recent advances in the knowledge of vitamin E have been confined in large measure to the field of chemistry. Details of this advance may be found in journals or books devoted to this subject.²⁰³ Evans and his associates²⁰⁴ expressed the

198 Chown, B., Lee, M., Teal, J., and Currie, R. On the Experimental Production of Nephritis in Rats by Means of Parathyroid Hormone and of Vitamin D, *J Path & Bact* **49**:273-290 (Sept) 1939.

199 Harris, R. S., Ross, B. D., and Bunker, J. W. M. Histological Study of Hypervitaminosis D. The Relative Toxicity of Vitamin D of Irradiated Ergosterol and Tuna Liver Oil, *Am J Digest Dis* **6**:81-83 (April) 1939.

200 Knapp, A. A. Vitamin-D Complex in Progressive Myopia. Etiology, Pathology, and Treatment, Preliminary Study, *A Research Ophth*, *Proc* **10**:80-88, 1939, Vitamin-D Complex in Progressive Myopia. Etiology, Pathology and Treatment, Preliminary Study, *Am J Ophth* **22**:1329-1337 (Dec) 1939.

201 Simpson, C. A., Ellis, F. A., and Kirby-Smith, H. Vitamin D in the Treatment of Acne, *Arch Dermat & Syph* **41**:835-837 (May) 1940. Mavnard, M. T. R. Vitamin Therapy in Dermatology with Particular Reference to Vitamin D in the Treatment of Acne and of Diseases Due to Altered Usage of Calcium, *ibid* **41**:842-857 (May) 1940. Thacker, E. A. The Treatment of Psoriasis with Various Vitamin D Preparations, *Illinois M J* **78**:352-360 (Oct) 1940.

202 Poer, D. H. Dihydrotachysterol, Parathormone and Vitamin D₂. Comparison of Their Values in the Treatment of Post-Thyroidectomy Hypocalcemic Tetany, *South M J* **33**:1174-1180 (Nov) 1940.

203 Smith, L. I. The Chemistry of Vitamin E, *Chem Rev* **27**:287-329 (Oct) 1940, Vitamin E, New York, Chemical Publishing Co., Inc., 1940.

belief that the following structural properties are necessary for the activity of vitamin E (1) a certain structural skeleton which will permit ready conversion of the substance to an oxidation-reduction system, and (2) accessory groups of such a nature as to provide solubility for absorption and transportation. Furthermore, the organism must have the ability to effect the necessary chemical transformation. Karrer²⁰⁵ demonstrated the importance in biologic activity of the long aliphatic side chain and methyl substitution in the aromatic nucleus. The tocopherol esters were shown to possess vitamin E activity equal to that of the parent tocopherol, with the added advantage that they are more stable to oxidation.²⁰⁶

Numerous procedures have been devised for the chemical estimation of the tocopherols, but most of these methods have the same fundamental shortcoming in that they do not distinguish the various tocopherols that differ in biologic activity.

In contrast to the remarkable strides in the chemical field, little has been added to the knowledge of the physiologic role of vitamin E in living organisms. Progress has been hampered by many experimental difficulties, and results and conclusions are not in agreement. As has been found to be true in regard to other vitamins, the possibility seems to exist that the tocopherols and their homologues may possess some function in the general cellular metabolism of the animal body, but this has not been proved. Pappenheimer²⁰⁷ listed the nutritional disorders of various laboratory animals deficient in vitamin E as (1) nutritional encephalomalacia of chicks, (2) nutritional myopathy of ducklings, (3) nutritional myopathy of the gizzard of turkeys, (4) nutritional muscular dystrophy of guinea pigs and rabbits and (5) muscular dystrophy of young rats. He expressed the belief that whereas no forecast can be made regarding the relation of these conditions to human disorders, there is enough evidence "to justify a cautious empiricism." He suggested as one of the significant lessons from his work the fact that a partial deficiency of vitamin E in the mother may manifest itself only in the offspring. He suggested further that this fact may help to explain

204 Evans, H. M., Emerson, O. H., Emerson, G. A., Smith, L. I., Ungnade, H. E., Prichard, W. W., Austin, F. L., Hoehn, H. H., Opie, J. W., and Wawzonek, S. The Chemistry of Vitamin E. XIII. Specificity and Relationship Between Chemical Structure and Vitamin E Activity, *J. Organ. Chem.* **4**: 376-388 (Sept.) 1939.

205 Karrer, P. Vitamin E und verwandte Verbindungen, *Helvet. chim. acta* **22**: 334-360, 1939.

206 Demole, V., Isler, O., Ringier, B. H., Salomon, H., and Karrer, P. Ueber Ester des α -Tocopherols, *Helvet. chim. acta* **22**: 65-68, 1939.

207 Pappenheimer, A. M. Certain Nutritional Disorders of Laboratory Animals Due to Vitamin E Deficiency, *J. Mt. Sinai Hosp.* **7**: 65-76 (July-Aug.) 1940.

the observed familial and hereditary characteristics of certain nervous and muscular disorders of human beings

Results of animal experiments during the past year have added little to Pappenheimer's ²⁰⁷ list, and a good share of the work has been related to the vitamin E activity of various tocopherols and their derivatives. Pappenheimer, Goettsch and Karsubova ²⁰⁸ were able to prevent muscular dystrophy in young rats by section of the peripheral nerves, subsequent experiments by the same investigators revealed that section of the achilles tendon was equally effective in preventing dystrophy of the gastrocnemius muscle and that the loss of muscle tonus rather than the loss of the nerve supply itself appeared to afford protection. Elvehjem and his associates ²⁰⁹ produced muscular dystrophy among dogs by a diet deficient in vitamin E, but only when the animals were under the added physical strain of gestation and lactation.

The relation of vitamin E to the reproductive organs of laboratory animals has been recognized for several years, no recent contributions on the relation of the various conditions produced by lack of vitamin E to human sterility have appeared. Results of experimental work attempting to relate deficiency of vitamin E to dysfunction of the pituitary body are at variance and permit no conclusions ²¹⁰

Evans ²⁰⁴ raised the following questions, which must be answered before the physiologic role of vitamin E can be understood

1 What is the "specificity" of chemical structure in vitamin E responses, and are different portions of the tocopherol molecule necessary for neuromuscular and reproductive normality? 2 What is the actual mode of action of the vitamin in the physiology of embryos, seminiferous epithelium and neuromuscular apparatus? 3 What is the cause of death in E-free sucklings and how does spontaneous recovery ensue? 4 What analogous human clinical conditions exist either of myogenic or neurogenic origin?

Clinical Use—During the past year, clinicians have concerned themselves with the possible benefit of vitamin E to various neuromuscular disorders. Bicknell ²¹¹ reported satisfactory improvement in cases of

208 Pappenheimer, A. M., Goettsch, M., and Karsubova, C. Effect of Nerve Section upon Development of Nutritional Muscular Dystrophy in Young Rats, *Proc Soc Exper Biol & Med* **43** 313-316 (Feb) 1940

209 Anderson, H. D., Elvehjem, C. A., and Gonce, J. E., Jr. Vitamin E Deficiency in Dogs, *Proc Soc Exper Biol & Med* **42** 750-755 (Dec) 1939

210 Koneff, A. A. Pituitary Changes in Male Rats Reared and Maintained on "Pure" Diets With and Without Vitamin E, *Anat Rec* **74** 383-399 (Aug 25) 1939. Drummond, J. C., Noble, R. L., and Wright, M. D. Studies on the Relationship of Vitamin E (Tocopherols) to the Endocrine System, *J Endocrinol* **1** 275-286 (Nov) 1939

211 Bicknell, F. Vitamin E in the Treatment of Muscular Dystrophies and Nervous Diseases, *Lancet* **1** 10-13 (Jan 6) 1940

amyotrophic lateral sclerosis and progressive muscular dystrophy Wechsler ²¹² treated 2 patients who had early amyotrophic lateral sclerosis and observed excellent results Spies and Vilter ²¹³ reported improvement in occasional cases of amyotrophic lateral sclerosis in which synthetic alpha tocopherol was used Stone ²¹⁴ noted definite improvement in 5 cases of muscular dystrophy and in several cases of muscular atrophy after wheat germ oil was added to the diet, he stated that addition of the vitamin B complex enhanced the therapeutic value of vitamin E Vilter and his associates ¹²² reported more spectacular remissions in a case of acute arsenical peripheral neuritis after treatment with both pyridoxine (vitamin B₆) and alpha tocopherol than when the former was used alone

In contradiction to these observations, Shelden, Woltman and one of us (H R B) ²¹⁵ were unable to demonstrate any improvement in 8 patients with progressive muscular dystrophy, 6 with amyotrophic lateral sclerosis and 4 with progressive muscular atrophy These patients were treated for three to six months with combined wheat germ oil and synthetic alpha tocopherol It is felt that further clinical evidence is needed to support the contention that lack of vitamin E is a primary factor in the causation of these various disorders

The use of vitamin E in the treatment of various disorders of the human reproductive system was thoroughly discussed in a report of the Council on Pharmacy and Chemistry of the American Medical Association, ²¹⁶ and the reader is referred to this publication for details of this subject Some of the conclusions follow

Claims that vitamin E (wheat germ oil) is of value in the treatment of menstrual disorders, failure of lactation and the vaginal pruritus after the menopause [and] in the prevention of habitual abortion cannot be accepted because of lack of convincing clinical evidence The published results of the treatment of habitual abortion with vitamin E are sufficiently encouraging to justify further clinical experiment

212 Wechsler, I S Recovery in Amyotrophic Lateral Sclerosis Treated with Tocopherols (Vitamin E) Preliminary Report, J A M A **114** 948-950 (March 16) 1940

213 Spies, T D, and Vilter, R W A Note on the Effect of Alpha-Tocopherol (Vitamin E) in Human Nutrition, South M J **33** 663-664 (June) 1940

214 Stone, S Treatment of Muscular Dystrophies and Allied Conditions Preliminary Report on Use of Vitamin E (Wheat Germ Oil), J A M A **114** 2187-2191 (June 1) 1940

215 Shelden, C H, Butt, H R, and Woltman, H W Vitamin E (Synthetic Alpha-Tocopherol) Therapy in Certain Neurologic Disorders, Proc Staff Meet, Mayo Clin **15**:577-580 (Sept 11) 1940

216 The Treatment of Habitual Abortion with Vitamin E, report of the Council on Pharmacy and Chemistry, J A M A **114** 2214-2218 (June 1) 1940

VITAMIN K

Chemical and Physiologic Properties—Vitamin K₁ is a synthetic compound identical with 2-methyl-1, 4-naphthoquinone except that the vitamin bears a phytyl side chain in the 3 position (2-methyl-3-phytyl-1,4-naphthoquinone). The synthetic product is also identical with natural vitamin K₁, which is obtained from alfalfa,²¹⁷ although it is not utilized so rapidly by the body as 2-methyl-1, 4-naphthoquinone.²¹⁸ The correct empiric formula now proposed for vitamin K₂ is C₄₁H₆₀O₂.²¹⁹

Most of the advances in the chemistry of vitamin K have been made in the study of naphthoquinone derivatives. Of those investigated, 2-methyl-1,4-naphthoquinone has proved to possess the most marked antihemorrhagic activity.²²⁰ Ansbacher and Fernholz²²¹ were the first to show that this compound is as active as vitamin K, and this work now has been amply confirmed. In an extensive study of substituted alpha naphthoquinones, Binkley and his co-workers²²² found that the degree of activity of these substances varied widely, the highest activity being about a fifth that of pure vitamin K₁. Doisy and associates²²³ reported that only 1,4-naphthoquinone and compounds which on oxidation in the organism might yield 1,4-naphthoquinone have vitamin K activity. Besides these authors, others²²⁴ have isolated several water-soluble compounds which have a high antihemorrhagic activity.

Little is known about the physiologic effect of vitamin K. It is well established that it plays some vital role in the metabolism of prothrombin, but its exact mode of action is unknown.

217 Fieser, L. F. Synthesis of Vitamin K₁, J Am Chem Soc **61** 3467-3475 (Dec.) 1939. Emmett, A. D., Brown, R. A., and Kamm, O. Comparison of the Antihemorrhagic Activity of Natural and Synthetic Vitamin K₁ with the Proposed Standard 2-Methyl-1,4-Naphthoquinone, J Biol Chem **132** 467-468 (Jan.) 1940.

218 Ansbacher, S. Vitamin K, J Biol Chem **133** iii-iv (May) 1940.

219 Fieser, L. F. Synthesis of 2-Methyl-3-Phytyl-1,4-Naphthoquinone, J Am Chem Soc **61** 2559-2561 (Sept.) 1939. Binkley, S. B., McKee, R. W., Thayer, S. A., and Doisy, E. A. Structure of Vitamin K₂, J Biol Chem **133** xii-xiii (May) 1940.

220 Almquist, H. J., and Klose, A. A. Antihemorrhagic Activity of 2-Methyl-1,4-Naphthoquinone, J Biol Chem **130** 787-789 (Oct.) 1939.

221 Ansbacher, S. and Fernholz, E. Simple Compounds with Vitamin K Activity, J Am Chem Soc **61** 1924-1925 (July) 1939.

222 Binkley, S. B., Cheney, L. C., Holcomb, W. F., MacCorquodale, D. W., Thayer, S. A., and Doisy, E. A. The Vitamin K Activity of Some Substituted α -Naphthoquinone and of Some Related Compounds, abstracts read before the Division of the Biological Chemistry of the American Chemical Society, Boston, Sept. 11-15, 1939.

223 Doisy, E. A., MacCorquodale, D. W., Thayer, S. A., Binkley, S. B., and McKee, R. W. The Isolation, Constitution and Synthesis of Vitamin K₁, Science **90** 407 (Nov. 3) 1939.

224 Moore, M. B., and Kirchmeyer, F. J. Personal communication to the authors.

Among human beings serious untoward reactions have not been observed after reasonable therapeutic doses of either natural or synthetic compounds of vitamin K. As much as 5 mg of 4-amino-2-methyl-1-naphthol hydrochloride has been administered intravenously in a single dose, and 40 mg has been administered intravenously to human beings within a period of nineteen days without the occurrence of any untoward reaction. In a period of thirty-one days, 40 mg of 2-methyl-1,4-naphthoquinone-3-sodium sulfonate was administered intravenously and 28 mg administered orally to 1 person without causing any untoward reaction, either during or after its administration.²²⁵ On the other hand, Koller²²⁶ observed that large doses (180 mg) of 2-methyl-1,4-naphthoquinone administered orally to human beings resulted in vomiting and porphyrinuria. When 30 mg of this substance per kilogram of body weight was injected intramuscularly into a dog, vomiting, porphyrinuria and albuminuria resulted. Molitor and Robinson²²⁷ also studied the acute and chronic toxicity of orally and parenterally administered vitamin K₁, phthiocol and 2-methyl-1,4-naphthoquinone. The oral lethal dose of phthiocol for mice was approximately 0.2 Gm per kilogram of body weight, and that of 2-methyl-1,4-naphthoquinone, 0.5 Gm per kilogram of body weight. In experiments conducted to determine chronic toxicity, it was noted that daily administration for thirty consecutive days of 0.35 Gm of phthiocol and of 0.5 Gm of 2-methyl-1,4-naphthoquinone per kilogram of body weight produced toxic reactions and that doses of 0.1 Gm of phthiocol and 0.35 Gm of 2-methyl-1,4-naphthoquinone per kilogram of body weight produced a marked decrease in the number of erythrocytes and the concentration of hemoglobin. Such effects were not observed after the administration of vitamin K₁.

It is now well established that a proper response to vitamin K depends on the integrity of the hepatic parenchyma. This was early established by Warner²²⁸ and by one of us (H. R. B.) and associates.²²⁹ Rhoads²³⁰ found that 15 per cent of a group of patients who had hepatic damage did not respond to the administration of synthetic substances which had vitamin K activity. At necropsy severe hepatic damage was

225 Butt, H. R., Snell, A. M., and Osterberg, A. E. Unpublished data.

226 Koller, F. Ueber die klinische Wirksamkeit von Naphtochinonderivaten (Vitamin K-Wirkung), *Schweiz med Wchnschr* **69** 1159-1161 (Nov 11) 1939.

227 Molitor, H., and Robinson, H. J. Oral and Parenteral Toxicity of Vitamin K₁, Phthiocol and 2 Methyl 1,4 Naphthoquinone, *Proc Soc Exper Biol & Med* **43** 125-128 (Jan) 1940.

228 Warner, E. D., in discussion on Butt, Snell and Osterberg²²⁹.

229 Butt, H. R., Snell, A. M., and Osterberg, A. E. Oral and Intramuscular Administration of Vitamin K in Hemorrhagic Diathesis of Obstructive Jaundice, *J A M A* **112** 879-880 (March 4) 1939.

230 Rhoads, J. E. Physiological Factors Regulating the Level of the Plasma Prothrombin, *Ann Surg* **111** 916 (May) 1940.

found Bollman and his associates²³¹ noted that rats whose livers were severely injured by chloroform intoxication did not respond in the usual manner to treatment with vitamin K. Similar observations were reported by others²³²

Methods of Measuring Prothrombin—The measurement of prothrombin in the circulating blood is still a prerequisite to the intelligent use of vitamin K. In an excellent review of the literature on prothrombin in the plasma and vitamin K, Brinkhous²³³ discussed in detail the various methods for measuring prothrombin. During the past year, the necessity of measuring the prothrombin in small quantities of blood obtained from newborn or premature infants has led to the development of several micromethods²³⁴

Prothrombin in Stored Blood—The level of prothrombin in stored blood has received considerable attention. It has been observed that citrated blood which is allowed to stand for any length of time ("bank blood") does not contain much prothrombin and is therefore of little value in the control of hemorrhage resulting from a deficiency of prothrombin²³⁵. In contrast to this observation, Belk and his associates²³⁶ found that Quick's prothrombin time of stored blood was moderately prolonged after ten days, but not after five days. In contrast, Lord and Pastore²³⁷ and Warner and his associates,²³⁸ using the quantitative

231 Bollman, J. L., Butt, H. R., and Snell, A. M. The Influence of the Liver on the Utilization of Vitamin K, *J. A. M. A.* **115** 1087-1091 (Sept. 28) 1940

232 Brinkhous, K. M., and Warner, E. D. Effect of Vitamin K on Hypoprothrombinemia of Experimental Liver Injury, *Proc. Soc. Exper. Biol. & Med.* **44** 609-610 (June) 1940

233 Brinkhous, K. M. Plasma Prothrombin. Vitamin K, *Medicine* **19** 329-416 (Sept.) 1940

234 (a) Kato, K. Micro-Prothrombin Test with Capillary Whole Blood. A Modification of Quick's Quantitative Method, *Am. J. Clin. Path.* **10** 147-153 (Feb.) 1940. (b) Quick, A. J. Determination of Prothrombin, *Proc. Soc. Exper. Biol. & Med.* **42** 788-789 (Dec.) 1939. (c) Bray, W. E., and Kelley, O. R. Prothrombin Studies, Especially in the Newborn, *Am. J. Clin. Path.* **10** 154-167 (Feb.) 1940. (d) Kelley, O. R., and Bray, W. E. Prothrombin Time Determinations, *J. Lab. & Clin. Med.* **25** 527-530 (Feb.) 1940. (e) Kato, K., and Poncher, H. G. The Prothrombin in the Blood of Newborn Mature and Immature Infants as Determined by the Micro Prothrombin Test, *J. A. M. A.* **114** 749-753 (March 2) 1940

235 Rhoads, J. E., and Panzer, L. M. The Prothrombin Time of "Bank Blood," *J. A. M. A.* **112** 309-310 (Jan. 28) 1939

236 Belk, W. P., Henry, N. W., and Rosenstein, F. Observations on Human Blood Stored at Four to Six Degrees Centigrade, *Am. J. M. Sc.* **198** 631-633 (Nov.) 1939

237 Lord, J. W., Jr., and Pastore, J. B. Plasma Prothrombin Content of Bank Blood, *J. A. M. A.* **113** 2231-2232 (Dec. 16) 1939

238 Warner, E. D., and Flynn, J. E. Absorption of Water-Soluble Vitamin K from Intestinal Tract, *Proc. Soc. Exper. Biol. & Med.* **44** 607-608 (June) 1940

prothrombin method of Warner, Brinkhous and Smith, observed that in stored blood maintained aseptically at 5 C disintegration of plasma prothrombin occurred gradually, a value of 50 per cent of normal was reached at the end of about three weeks. Similar results were also obtained by Ziegler and her associates²³⁹

Clinical Use of Vitamin K—Numerous reports have appeared during the past year which tend to establish the fact that vitamin K in the form of natural concentrates or pure synthetic products which exhibit antihemorrhagic activity is useful in the prevention and control of the hemorrhagic diathesis that frequently occurs among patients who exhibit hypoprothrombinemia.

The commercial availability of synthetic compounds which possess antihemorrhagic activity has led to the general use of these materials, in many instances as a substitute for the formerly employed concentrates of alfalfa and of fish meal. Several investigators²⁴⁰ reported the successful use of 2-methyl-1,4-naphthoquinone administered orally, intramuscularly and intravenously. In most cases, 1 to 4 mg of this compound, together with 5 to 10 grains (0.3 to 0.65 Gm) of animal bile salts, constituted an adequate daily oral dose. By the intravenous route, 1 to 2 mg was likewise an effective daily dose in most instances. The results as judged on the basis of all these reports are good except in those instances in which severe hepatic damage was present.

In the hands of most investigators,²⁴¹ a water-soluble compound, 4-amino-2-methyl-1-naphthol hydrochloride, has proved to be just as effective when given by the intravenous route as the derivative of

239 Ziegler, E. R., Osterberg, A. E., and Hovig, M. The Prothrombin Changes in Banked Blood, *J. A. M. A.* **114** 1341-1342 (April 6) 1940.

240 MacCorquodale, D. W., Cheney, L. C., Binkley, S. B., Holcomb, W. F., McKee, R. W., Thayer, S. A., and Doisy, E. A. The Constitution and Synthesis of Vitamin K₁, *J. Biol. Chem.* **131** 357-370 (Nov.) 1939. Macfie, J. M., Bacharach, A. L., and Chance, M. R. A. The Vitamin K Activity of 2-Methyl-1,4-Naphthoquinone and Its Clinical Use in Obstructive Jaundice, *Brit. M. J.* **2** 1220-1223 (Dec. 23) 1939. Butt, H. R., Snell, A. M., Osterberg, A. E., and Bollman, J. L. Treatment of Hypoprothrombinemia. Use of Various Synthetic Compounds Exhibiting Antihemorrhagic Activity (Vitamin K₁ Activity), *Proc. Staff Meet., Mayo Clin.* **15** 69-73 (Jan. 31) 1940. Rhoads, J. E., and Fliegelman, M. T. The Use of 2-Methyl-1,4-Naphthoquinone (a Synthetic Vitamin K Substitute) in the Treatment of Prothrombin Deficiency in Patients, *J. A. M. A.* **114** 400-401 (Feb. 3) 1940. Sharp, E. A. Vitamin K Activity of 2-Methyl-1,4-Naphthoquinone, *ibid.* **114** 439-440 (Feb. 3) 1940.

241 (a) Wilkie, D. P. D. Surgery of the Biliary Passages, *Tr. Med.-Chir. Soc. Edinburgh*, 1924-1925, pp. 50-64, in *Edinburgh M. J.*, March 25, 1925. (b) Emmett, A. D., Kamm, O., and Sharp, E. A. The Vitamin K Activity of 4-Amino-2-Methyl-1-Naphthol and 4-Amino-3-Methyl-1-Naphthol, *J. Biol. Chem.* **133** 285-286 (March) 1940. (c) Aggeler, P. M., Lucia, S. P., and Goldman, L. Effect of Synthetic Vitamin K Compounds on Prothrombin Concentration in Man, *Proc. Soc. Exper. Biol. & Med.* **43** 689-694 (April) 1940.

2-methyl-1,4-naphthoquinone In Butt and Snell's experience,²⁴² this compound given intravenously in doses of 1 to 2 mg has proved to be effective in reducing an elevated prothrombin clotting time. Untoward reactions have not followed its administration. As this compound is water soluble, the belief has been expressed that it may be administered orally without bile salts in the presence of biliary obstruction. Reports indicate that this can be done successfully both experimentally²³⁸ and clinically²⁴³.

It is now well established that in certain cases of severe hepatic damage response to vitamin K does not occur.²⁴⁴ It was observed that²⁴⁵ in cases of primary hepatic disease the prothrombin clotting time is not often more than forty-five to fifty seconds. To reduce this elevated prothrombin time to within normal limits often is a hopeless task, regardless of the amounts of vitamin K administered. It is well to remember that patients who have severe primary hepatic damage constitute a group who are perhaps not primarily deficient in vitamin K but whose livers have lost the ability to produce prothrombin even in the presence of adequate amounts of vitamin K. In our own experience, patients with an increased prothrombin time which does not respond to the administration of vitamin K must be observed carefully after any surgical procedure. This failure in response often indicates that the liver is so badly damaged that such interference as a surgical procedure may easily produce hepatic insufficiency. Although the prothrombin clotting time may remain increased after vitamin K has been administered, if a fatal hemorrhagic diathesis does occur, it apparently results not from hypoprothrombinemia but from some other cause.

It is now becoming well established that deficiency of prothrombin in the circulating blood develops in cases of intestinal disorders.²⁴⁶

242 Butt, H R, and Snell, A M. Unpublished data.

243 Smith, H P, and Owen, C A. The Absorption of Water-Soluble Vitamin K Without the Aid of Bile Salts, *J Biol Chem* **134** 783-784 (July) 1940. Butt and Snell²⁴².

244 Scanlon, G H, Brinkhous, K M, Warner, E D, Smith, H P, and Flynn, J E. Plasma Prothrombin and the Bleeding Tendency with Special Reference to Jaundiced Patients and Vitamin K Therapy, *J A M A* **112** 1898-1901 (May 13) 1939. Smith, H P, Ziffren, S E, Owen, C A, and Hoffman, G R. Clinical and Experimental Studies on Vitamin K, *ibid* **113** 380-383 (July 29) 1939. Warner²²⁸. Butt, Snell and Osterberg²²⁹. Rhoads²³⁰. Aggeler, Lucia and Goldman^{241c}.

245 Butt, H R, Snell, A M, and Osterberg, A E. The Preoperative and Postoperative Administration of Vitamin K to Patients Having Jaundice, *J A M A* **113** 383-390 (July 29) 1939.

246 Albright, F, and Stewart, J D. Hypovitaminosis of All Fat-Soluble Vitamins Due to Steatorrhea. Report of a Case, *New England J Med* **223** 239-241 (Aug 15) 1940. Mackie, T T. Vitamin K Deficiency in the Absence of Jaundice, *New York State J Med* **40** 987-995 (July 1) 1940. Weir, J F, Butt, H R, and Snell, A M. Further Observations on the Clinical Use of Vitamin K, *Am J Digest Dis* **7** 485-490 (Nov) 1940.

Apparently deficiency of prothrombin because of inadequate intestinal absorption usually developed in cases in which it was necessary to employ a limited diet or to withhold food and perform intestinal intubation in order to control an obstructive lesion. Profuse discharge from ileac stomas or severe chronic diarrhea further complicated the situation for many of these patients.

Vitamin K and the Newborn Infant—It is generally agreed that during the first few days of an infant's life a deficiency of prothrombin exists in the circulating blood, but the cause of this deficiency is still debated. Using their own micromethod, a modification of Quick's method, Kato and Poncher^{234e} reported that the prothrombin clotting time of the blood of newborn infants is for the most part high, particularly on the first day of life and that it averages forty-six and five-tenths seconds for the premature infant and forty-three and two-tenths seconds for the full term infant. A decrease in the prothrombin clotting time occurs as the infant grows older, so that by the end of the ninth or tenth day the clotting time of the full term infant averages twenty-five seconds. Similar observations were made by other investigators^{234c}.

Salomonsen and Nygaard²⁴⁷ reported that if extra feedings were started within two hours after delivery of the infant, subsequent development of hypoprothrombinemia could be prevented. These authors reasoned that early, extra feedings of the newborn may result in the hastening of metabolism of bacteria in the intestine, which creates a supply of vitamin K sufficient for the prevention of a relative transitory deficiency of prothrombin.

The treatment of hemorrhagic diathesis of the newborn has received considerable attention.²⁴⁸ On the basis of the work presented, it appears

247 Salomonsen, L., and Nygaard, K. K. The Prothrombin Content in Relation to Early and Late Feedings of the Newborn. A Preliminary Report, *Acta pædiat* **27** 209-218, 1939.

248 Waddell, W. W., Jr., and Guerry, D., III. The Role of Vitamin K in the Etiology, Prevention, and Treatment of Hemorrhage in the Newborn Infant, *J. Pediat* **15** 802-811 (Dec.) 1939. Kuhn, R., Wellenfels, K., and Weygand, H. Zur Spezifität des Vitamins K, *Naturwissenschaften* **27** 518-519 (July 28) 1939. Nygaard, K. K. Prophylactic and Curative Effect of Vitamin K in Hemorrhagic Disease of the Newborn (Hypoprothrombinemia Hemorrhagica Neonatorum). A Preliminary Report, *Acta obst. et gynec. Scandinav* **19** 361-370, 1939. Hellman, L. M., and Shettles, L. B. Factors Influencing Plasma Prothrombin in the Newborn Infant. Prematurity and Vitamin K. *Bull. Johns Hopkins Hosp* **65** 138-141 (July) 1939. Shettles, L. B., Delfs, E., and Hellman, L. M. Factors Influencing Plasma Prothrombin in the Newborn Infant. II. Antepartum and Neonatal Ingestion of Vitamin K Concentrate, *ibid* **65** 419-426 (Nov.) 1939. Andrus, W. DeW., and Lord, I. W., Jr. Correction of Prothrombin Deficiencies by Means of 2-Methyl-1,4-Naphthoquinone Injected Intramuscularly, *J. A. M. A.* **114** 1336-1337 (April 6) 1940. MacPherson, A. I. S., McCallum, E., and Haultain, W. F. T. Effect of Intrapartum and Neonatal Administration of Synthetic Vitamin K Analogues on the Newborn, *Brit. M. J.* **1** 839-844 (May 25) 1940.

that a dose of from 1 to 5 mg of 2-methyl-1,4-naphthoquinone, or any of the other synthetic quinone compounds mentioned, is sufficient in most instances to control hemorrhagic diseases among the newborn, and if this dose is administered at time of birth it will prevent transitory hypoprothrombinemia. One must remember that there can also be failures in treatment with substances from this group of compounds, provided sufficient hepatic damage has occurred. In the articles just referred to, the effect of the administration of vitamin K and synthetic compounds which exhibit vitamin K activity on pregnant women and the subsequent effect on the newborn were discussed. On the basis of these studies, it appeared that the same dose of vitamin K as that which is administered to newborn infants, if administered to the mother twelve to twenty-four hours prior to delivery, resulted in the baby having a higher value for prothrombin than is normally present. These synthetic compounds are apparently effective when administered either orally or parenterally, and toxic effects have not been noted on either the mother or the infant.

GENERAL FEATURES IN NUTRITION

There is little doubt that the American public, because of the press and advertising on the radio, is becoming tremendously concerned with its health. These and many other factors have undoubtedly accounted for the marked increase of self medication with vitamin preparations during the past two years. In this connection, Sebrell,²⁴⁹ in a recent article, related some interesting and timely facts. He pointed out that of the \$53,790,000 spent by the public for vitamin preparations during 1938, \$21,000,000 was spent for products which did not conform with either the Pharmacopoeia of the United States or with the National Formulary. The figure for 1935 was only about \$4,700,000. Sebrell²⁴⁹ expressed the belief that these figures indicate more nearly the success of the advertising campaign than the sales due to real need. No doubt people with money do purchase such preparations, but they certainly do not constitute the large group of the population which is most likely to be on a deficient diet. It was reported that three of every ten families in cities and villages do not have enough money to spend for the foods which would constitute a good, complete and adequate diet. From investigations by others, it appears that a large proportion of the diets of rural families are poorly supplied with both fruits and vegetables. There is no doubt that money solves the problem of getting enough to eat, but it does not offer assurance that the nutritional values of the diets selected will be satisfactory. It is still a good policy to obtain vitamins from the grocery store rather than from the drug store.

²⁴⁹ Sebrell, W. H. Nutritional Diseases in the United States, *J. A. M. A.* **115** 851-854 (Sept. 7) 1940.

Although concentrated forms of vitamins may be used under many conditions, there seems little reason for using a concentrate merely because the vitamin is present in concentrated form. As Elvehjem²⁵⁰ pointed out, 1 Gm of a product containing 100 units of a vitamin may not be any more valuable than 100 Gm of a food containing 1 unit per gram. In most cases, 100 Gm of food would be much better since it also might contain 100 units of ten different factors.

Fortification of Food—There are many reasons to believe that American dietaries with respect to content of many nutrient materials²⁵¹ are as a whole unsatisfactory. For these reasons a feeling has arisen during the past few years that perhaps a distinct justification for fortification of foods with vitamins and minerals exists. There seems to be no fundamental objection to the addition of synthetic vitamins to food materials, but the commercial fortification of foods must be carefully controlled.²⁵² Great Britain already has fortified margarine with vitamin A and restored calcium and thiamine hydrochloride to flour. Because of this the belief is expressed that ill effects from a deficiency of calcium compounds and vitamin B₁ will be minimized, notwithstanding lower rations.²⁵³ This subject is receiving consideration by those responsible for national defense in the United States.

There are many valid objections to the fortification of foods. As Sebrell²⁵⁴ pointed out, such a procedure in all probability not only would fail to be of any material value in the prevention of the diseases of deficiency because the fortified foods would not be available to the part of the population in greatest need of them, but also would be an economically wasteful procedure because it would unnecessarily increase the cost of these foods for persons whose diet is already adequate. Instead of this, he suggested that the situation might be corrected by trying to build up an association between good health and a colorful diet. This author and many others have expressed the opinion that the problem of deficiency diseases will never be solved by fortifying foods, but that it can be solved by education and by making available to every one the widest variety of natural unrefined foods at the lowest possible prices. It is amusing, as Elvehjem²⁵⁰ pointed out, that many more objections

250 Elvehjem, C. A. The Vitamin B Complex in Normal Nutrition, *J. Am. Dietet. A.* **16** 646-654 (Aug.-Sept.) 1940.

251 Cowgill, G. R. The Need for the Addition of Vitamin B₁ to Staple American Foods, *J. A. M. A.* **113** 2146-2151 (Dec. 9) 1939.

252 Morgan, A. F. Fortification of Foods with Vitamins and Minerals, *Milbank Memorial Fund Quart.* **17** 221-229 (July) 1939. Elvehjem²⁵⁰.

253 Vitamins for War, editorial, *J. A. M. A.* **115** 1198-1199 (Oct. 5) 1940.

254 Sebrell, W. H. The Public Health Aspects of the Fortification of Foods with Vitamins and Minerals, *Milbank Memorial Fund Quart.* **17** 241-247 (July) 1939.

are raised when a commercial company wants to add a vitamin to a food than when new processing methods are introduced which are known to be destructive to the vitamin

Effects of Cooking and Freezing on Foods—In an extensive study, Aughey and Daniel²⁵⁵ observed that destruction of thiamine amounted to as much as 22 per cent in foods boiled in water and that additional amounts up to 15 per cent dissolved in the cooking water. When the cooking water was discarded, the total losses of thiamine in vegetables frequently amounted to approximately 20 to 35 per cent. Roasting caused the loss of 43 per cent of the thiamine in pork loin. Cooking of whole grain cereals in a double boiler did not destroy the thiamine. In the light of their analysis, the authors pointed out some interesting household hints. On a serving basis, baked potatoes, including the skin, ranked higher in content of thiamine than did cooked whole wheat or oat cereal. Even boiled potatoes, spinach and carrots may be classed as furnishing an amount of thiamine comparable to those amounts supplied by cooked cereals. One slice of whole wheat bread contains approximately the same quantity of thiamine as one serving of these vegetables or cereal foods, and one serving of lean pork loin cooked either as chop or roast furnishes a plentiful daily allowance of thiamine for the adult.

Rose,²⁵⁶ in an extensive study, reported that the number of micro-organisms in food apparently is reduced greatly by quick freezing but that after thawing the organisms increase rapidly. For this reason it is suggested that such foods should be cooked either without thawing or soon afterward. The values of vitamin A in food are conserved by storage at low temperatures, vitamin B₁, likewise, is not affected by the freezing itself, but considerable loss may occur in the blanching of vegetables which have a tendency to lose their content of thiamine by cooking. Practically no riboflavin was lost in the quickly frozen vegetables which were investigated. The ascorbic acid in fruits also appeared to be conserved by freezing.

255 Aughey, E., and Daniel, E. P. Effect of Cooking upon the Thiamin Content of Foods, *J. Nutrition* **19** 285-296 (March) 1940.

256 Rose, M. S. The Effect of Quick Freezing on the Nutritive Values of Foods, *J. A. M. A.* **114** 1356-1361 (April 6) 1940.

News and Comment

The Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation—Eighty-one applications for grants were received by the trustees of the Ella Sachs Plotz Foundation during 1940. Fifty-one of these came from the United States and the other thirty from fifteen different countries in Europe, Asia, North America and South America. The total number of grants made during this year was twenty-three, one of these being a continued annual grant.

In the seventeen years of its existence the Foundation has made three hundred and ninety-four grants, which have been distributed to investigators in Arabia, Argentina, Austria, Belgium, Brazil, Canada, Chile, China, Czechoslovakia, Denmark, Egypt, Estonia, Finland, France, Germany, Great Britain, Greece, Hungary, India, Iraq, Italy, Latvia, Lebanon, Netherlands, North Africa, Norway, Palestine, Poland, Portugal, Rumania, South Africa, Sweden, Switzerland, Syria, Venezuela, Yugoslavia and the United States.

During the present great need for funds, grants will be given in the sciences closely related to medicine without reference to special fields. The maximum size of grants will usually be less than \$500.

Applications for grants to be held during the year 1941-1942 must be in the hands of the executive committee before April 1941. There are no formal application blanks, but letters asking for aid must state definitely the qualifications of the investigator, an accurate description of the research, the size of the grant requested and the specific use of the money to be expended. In their requests for aid, applicants should state whether they have approached other foundations for financial assistance. It is highly desirable to include letters of recommendation from the directors of the departments in which the work is to be done. Only applications complying with the foregoing conditions will be considered.

Applications should be sent to Dr. Joseph C. Aub, Collis P. Huntington Memorial Hospital, 695 Huntington Avenue, Boston, Mass., U. S. A.

John Phillips Memorial Award for 1941—Dr. William Christopher Stadie, associate professor of research medicine at the University of Pennsylvania, has been awarded the John Phillips Memorial Medal for 1941 for his significant contributions to the knowledge of anoxia, cyanosis and the physical chemistry of hemoglobin, and more especially for his recent studies on fat metabolism in diabetes mellitus.

This award was established by the American College of Physicians in 1929, to be given periodically for some outstanding piece of work in internal medicine, including not only clinical science but all of those subjects which have a direct bearing on the advancement of clinical science. The work must have been done in whole or in part in the United States or in Canada.

Nominations for the award are made to the Committee on Fellowships and Awards of the American College of Physicians. The recipient must file with the College a written account of his work and present his results as a paper before the next annual session, at which time the award of a bronze medal is made by the president of the College.

Annual Meeting of the American Public Health Association—The seventieth annual meeting of the American Public Health Association will be held Oct 14-17, 1941, in Atlantic City, N J, in the Convention Hall. Residence headquarters will be the Hotel Traymore.

A committee responsible for entertainment, inspection trips and other local aspects of the meeting is being formed under the direction of Dr S L Salasin, Health Officer of Atlantic City.

The following related organizations will meet with the American Public Health Association: the American School Health Association, the International Society of Medical Health Officers, the Association of Women in Public Health, the Conference of State Sanitary Engineers, the Conference of Municipal Public Health Engineers and the Conference of State Provincial Public Health Laboratory Directors.

The sixty-ninth annual meeting, held in Detroit in October 1940, attracted an attendance of more than 3,100 from all parts of the United States, and from Canada, Cuba and Mexico.

Book Reviews

Physical Diagnosis By Ralph H Major, M D, Professor of Medicine in the University of Kansas Second edition, revised Price, \$5 Pp XIV + 464, with 437 illustrations Philadelphia and London W B Saunders Company, 1940

In 1938, a year after the first edition of this book had made its appearance, a certain teacher was about to commence a course in physical diagnosis with an enthusiastic class. The students asked for a textbook which they could afford to buy in order to read, study and interline their copies. Their teacher cast about for a likely candidate. He was pleased by Major's book by its appearance, illustrations and format, by its historical allusions, by its bibliographic references at the end of each chapter, above all, by its lucidity and charm of literary style. Not wishing to be handed a pig in a poke, he attempted to learn what others thought of it. Reviewers on the whole were complimentary. In the *Far West, California and Western Medicine* (46 14 [March] 1937) praised it highly. The less exuberant *Journal of the American Medical Association* (109 232 [July 17] 1937) and *Annals of Internal Medicine* (11 1916 [April] 1938) were not quite so flattering. There were a few minor faults with the book, admittedly, but on the whole these periodicals gave it favorable consideration. Naturally, that supercilious old maid from the Back Bay could be expected to do no more than turn up her nose at a newcomer. In a locality where Cabots speak only to Lowells, a textbook from the Middle West was intrusive. It could not compare with one of local breeding and, as all Boston knew, the twelfth edition of Richard Cabot's "Physical Diagnosis," with an imprint of the Massachusetts General Hospital on the title page, was about to make a bow. Thus the *New England Journal of Medicine* (216 726 [April 22] 1937) was aloof. Very coldly, it said that Major's book could not be recommended to students.

This particular teacher was not discouraged. He went through Major's book chapter by chapter with his class, comparing its illustrations with actual cases, making students look up references and read original articles or demonstrate on themselves or on patients the various physical signs described. In general he used the book happily as a trephine by which to drill into his pupils' heads the fundamentals of a sound knowledge of the art of physical diagnosis. The end result of this operation appeared to be eminently successful. The students not only learned but enjoyed the process.

The second edition of the book is better than the first. The author has listened wisely to advice from friends and, better still, to criticism from students. Thus the second edition is more polished than its predecessor, a better instrument for teaching and a keener-edged tool for the purpose of invading skulls a little thick. Teachers and students who still believe that a textbook on physical diagnosis is of use in medical pedagogy will welcome this edition with open arms. It warrants high recommendation.

Virus and Rickettsial Diseases With Especial Consideration of Their Public Health Significance Harvard School of Public Health Symposium Volume Price, \$6.50 Pp 907 Cambridge, Mass Harvard University Press, 1940

A symposium on virus and rickettsial diseases was held in June 1939 in Boston under the auspices of the Harvard School of Public Health. This volume is an amplified record of the thirty-four papers presented at that meeting. In view of the many recent developments in the field of the virus and rickettsial diseases, this volume should be welcome at the present time. It has been some years since any comprehensive work covering this field has been published in the English language.

The following virus and rickettsial diseases affecting man are discussed: variola, vaccinia, measles, mumps, dengue fever, venereal lymphogranuloma, influenza, psittacosis, poliomyelitis, epidemic encephalitis, equine encephalomyelitis, rabies, lymphocytic choriomeningitis, louping ill, yellow fever, the typhus fever group, the spotted fever group and the tsutsugamushi disease group. The review of these diseases is well carried out. The role of animals as reservoirs for certain of these diseases is considered, and such details as are known of the relation of the animal to the human disease are presented. It seems curious that inclusion blennorrhoea and trachoma are not considered, whereas a lecture is devoted to a disease of animals not affecting man, distemper.

As important as the discussions of specific diseases are the papers on epidemiology, immunology, physical and chemical properties of viruses, insect vectors and clinical diagnosis and complications of the various diseases. When methods of prevention or treatment are known, these are described. One paper deals with the prevention and modification of measles, and there are two papers on the preparation and use of specific vaccines. Pertinent to the general subject matter is a paper presenting a scholarly discussion of the absorption of toxic and infectious material from the respiratory tract.

Most of the authors of the various papers are associated with Harvard University. Their writings carry the weight of authority and are straightforward and accurate. Enough historical data are given to furnish the general reader with a picture of the development of the knowledge of the different subjects.

The references listed at the end of each article are well chosen and include those which are most important.

The book has no general index, which is something of a disadvantage. The material is accessible, however, by means of the table of contents, which gives the paging of the various papers, and by means of a rather complete outline which heads each paper and gives the paging of each topic in that paper. The binding is good and the print readable.

This book does not contain detailed descriptions of the technical methods used in virus investigation and is not primarily designed for the trained laboratory worker. It is a practical and scientific presentation of the present knowledge of diseases caused by viruses and rickettsias and should be of value to public health officers and to physicians who deal with infectious diseases.

La créatine, étude physio-pathologique By Jean Vague and Jean Dunau
Price, \$1.40 Pp 185 Paris Masson et Cie, 1939

In this monograph the authors have undertaken, with a high degree of success, to survey and interpret the present status of knowledge with regard to the chemistry, physiology and pathology of creatine and creatinine. Although emphasis is placed on developments in the subject since the discovery of phosphocreatine, the historical background has not been neglected, and the book is actually a review of the entire field. Preliminary chapters deal with the chemistry, determination and distribution of these compounds. A section is devoted to the relation of creatine to phylogenetic and ontogenetic development. The problem of the precursors of creatine is discussed and left as an open and important question still to be answered. In the following chapters, by means of an exposition of experimental and clinical observations, such subjects are treated as the role of creatine in the body, especially as an essential element in metabolism in muscle, and also as a possible essential in all cells, its relation to other organs, to diet and to the metabolism of carbohydrates, its storage and elimination and many other phases of its part in the organism. A picture is built up of a creatine cycle, controlled by a complex of factors, change in any one of which may lead to abnormality in the metabolism of creatine. Creatinine, as probably the sole end product of creatine, is a part of the picture. The authors state the belief that the derivation of urinary creatinine from creatine has been established and that at the present time the presence of true creatinine in the blood must be assumed. However, the anomalous behavior of the compound in blood under certain conditions remains

unexplained. The book concludes with an outline of the clinical significance which, according to the authors, may be attached to determinations of creatine and creatinine in blood and urine. Medical aspects are emphasized throughout.

This book is an interpretation as well as a review. Some of the conclusions may be questioned. For the most part a careful distinction is made between well established theories and those which are still largely hypothetic. Authorities are abundantly cited by name, and an international acquaintance with the field is manifested. The bibliography lists over 500 titles, including only publications since 1934. The reader is referred to the bibliographies of Hunter (1928) and Kayser (1934) for earlier work. A page index to authors cited in the text and a subject index (somewhat too brief) are included.

The Diagnosis and Treatment of Diseases of the Esophagus By P. P. Vinson, M.D. Price, \$4.00. Pp. 206. Springfield, Ill., and Baltimore: Charles C. Thomas, 1939.

This book meets a long-felt need for a short, concise description of diseases involving the esophagus. While several excellent books dealing with diseases of the esophagus are available, they include the entire field of pulmonary and esophageal diseases, and a great portion of such books deal with the technical phases of esophagoscopy and surgical procedures. The author has dealt with the subject in a manner that is very readable and understandable, both to the specialist and to the general practitioner. He has made a special effort to describe the various types of esophageal disease and the forms of treatment in the most simple and understandable way. He has included numerous excellent illustrations to show the various diagnostic and therapeutic procedures.

The author has had an unusual experience with the various forms of esophageal disease and has stressed the various pitfalls that may be encountered in diagnosis and treatment. While many readers may disagree with his selection of instruments for carrying out the various procedures, in the author's hands his instruments have been found eminently satisfactory. Some criticism might be made of the fact that he is prone in some instances to overlook the importance of esophagoscopy in the diagnosis of esophageal disease. He does this, however, in an effort to stress the importance of avoiding unnecessary instrumentation.

He has handled each type of disease of the esophagus in a separate chapter, discussing the symptoms and methods of diagnosis and treatment. The chapters dealing with carcinoma of the esophagus, cicatricial stricture, cardiospasm and hysterical dysphagia are especially worthy of notice.

The last chapter is given over to a description of gastroscopy. The author has not, however, gone into the subject in any detail, and undoubtedly he does not regard gastroscopy as an essential element in the diagnosis and treatment of esophageal disease.

Endocrine Gynecology By E. C. Hamblen, M.D. Price, \$5.50. Baltimore: C. C. Thomas, Publisher, 1939.

This volume is the best that the reviewer has read on the subject of endocrine disturbances in the female. The excellent organization, clarity of style, abundance of material and generous number of unique illustrations of great merit are particularly noteworthy.

The author discusses fully the physiologic principles and properties of the hormones of the glands of internal secretion, special emphasis being placed, naturally, on the sex hormones of the pituitary gland and on the sterols secreted by the ovaries. The physiology of normal menstruation as well as bleeding, cyclic or otherwise, is covered in an extensive and thorough discussion.

The laboratory method used for diagnostic purposes in cases of endocrine disturbances is described in detail and evaluated fully. The technic of endometrial biopsy and that of tubal insufflation are set forth, and the possible information to

be derived by such procedures is extensively discussed. The various endocrinopathies found in the female and the treatment of each are described, and statements are made as to what results may be expected.

The chapters on the endocrinal aspects of functional sterility and of gestation abnormalities are commendable.

This book is replete with material that will be of value to the endocrinologist, the gynecologist, the surgeon, the general practitioner and other physicians. Throughout the volume is reflected the author's extensive knowledge of the subject and experience in dealing with gynecologic endocrinologic problems.

A full and complete bibliography adds to the value of the book.

There are both an authors' index and a subject index.

Das menschliche Knochenmark By Karl Rohr, M D, Private Lecturer in Medicine, University of Zurich. Price, 37 marks. Pp 286, with 217 illustrations. Leipzig: Georg Thieme, 1940.

This is an excellent monograph. It discusses in an interesting manner everything which concerns the bone marrow: its embryology, anatomy, physiology and pathology, the character of the cells to be found in it and the varying pictures produced in it by different pathologic conditions.

The author was trained by Naegeli. Evidently he is a keen hematologist, having inherited much of his master's enthusiasm, and has enjoyed the putting together of this book. He has approached his task logically. There is first a short chapter on the medical history of the bone marrow, then a meticulous account of the technic of sternal puncture and finally chapters telling in detail the story of what properly conducted studies of bone marrow reveal.

The illustrations deserve comment, for the book is so well and attractively illustrated that the pictures alone are worth studying regardless of the text. Many of the figures are photomicrographs, beautifully clear and with excellent legends. Some are colored pictures, bringing out in diagrammatic and semi-diagrammatic form the development of the various marrow cells. Also, there are easily understandable tables and graphs appended, which demonstrate the modern hemogram and reveal how careful study of marrow cells and blood smears can be of great clinical usefulness.

Last of all is a good bibliography. It is predominantly European but gives due reference to the work of American hematologists.

On the whole, the author has compressed into a relatively short monograph a great deal of useful information. He deserves highest praise for completing a book which cannot fail to interest the general reader and yet at the same time is a useful reference work to the student or specialist whose chief occupation is to learn more of the peculiarities of the human bone marrow.

Vitamin D: Chemistry, Physiology, Pharmacology, Pathology, Experimental and Clinical Investigations By C. I. Reed, A. M., Ph. D., Associate Professor in Physiology, H. C. Struck, M. S., Ph. D., Associate in Physiology, and I. E. Steck, M. S., M. D., Instructor in Physiology and in Medicine, Departments of Physiology and Medicine, College of Medicine, University of Illinois. Price, \$4.50, cloth. Pp 389. Chicago: University of Chicago Press, 1939.

This monograph is an excellent review and evaluation of the recent literature on vitamin D and includes, in addition, the results of numerous investigations by the authors.

The chemistry and various forms of the vitamin and the methods of chemical and biologic assay are first discussed. Subsequent chapters deal with the physiology of vitamin D and its relation to rickets and to the parathyroid glands. The influence of vitamin D on energy metabolism, mineral metabolism, resistance to infection and blood constituents is considered in detail. Two chapters are devoted to the toxic effects of large doses of various forms of this vitamin. Good results

are reported from the use of vitamin D in the treatment of arthritis, and other possible therapeutic applications are indicated. Throughout the book emphasis is placed on problems which need further investigation. When controversial subjects are discussed, tentative interpretations are offered but no final conclusions are drawn. There is an excellent and extensive bibliography, which should be extremely useful to any one interested in research in this field. The book should be especially valuable to the physiologist and to the clinician interested in diseases of nutrition and metabolism.

Bothman's Fundus Atlas By Louis Bothman, M.D., and Reuel W. Bennett
Price, \$17 Pp 53 Chicago Year Book Publishers, 1939

Bothman's "Fundus Atlas" presents fifty original stereoscopic photographs of congenital anomalies and diseases of the fundus. These are mounted on cards, the photograph of the lesion being of the fundus given in duplicate accompanied with a history of the patient. There is also an excellent description of what is seen in the fundus in question.

Obviously the atlas is for the use of the ophthalmologist in teaching students, but it should be of immense service to the internist. To the medical student the ophthalmoscope has become almost as important an adjuvant to his diagnostic armamentarium as the otoscope, tongue depressor or reflex hammer. The student is taught to recognize the commoner ophthalmoscopic findings indicative of constitutional organic disease, but frequently some abnormality is noted which may be purely local. The teacher of internal medicine who is familiar with Bothman's "Fundus Atlas" can make the diagnosis and show to the student a close approximation of the lesion.

In addition to being of service to the teaching unit, the "Fundus Atlas" should be of great help to the practitioner who regularly uses the ophthalmoscope, as every practitioner should.

Pflanzliche Rohkostdiät By Ulrich Gruninger and Hanna Gettler Price
3.60 marks Pp 90 Stuttgart Ferdinand Enke, 1939

Diets of raw food, especially vegetables and fruit, are discussed and advised, particularly for children. A sample diet for a day is as follows: breakfast, strawberries and walnuts, lunch, radishes, salad, peas and cherries, evening meal, cucumbers, chicory salad, celery, bananas and dates. These diets are advised for various pathologic conditions, including diabetes of children, in connection with which no mention is made of insulin.

The reviewer had some difficulty in reading the old Gothic script which is used in this book.

Sexual Pathology: A Study of Derangements of the Sexual Instinct New Revised Edition By Magnus Hirschfeld, M.D. Price, \$2.95 Pp 368 New York Emerson Books, Inc., 1940

This book, written in a semipopular style, deals with aberrations of sexual instinct and behavior largely from a clinical standpoint. It is the reviewer's impression that the discussion is not based on the most profound modern psychiatric knowledge in this field, and many of the lengthy case reports could perhaps be replaced to advantage by more systematic discussions of the principles involved in these aberrations, both psychic and somatic.

Clinique et physiopathologie des maladies coeliaques By Robert Dubois Price, 80 francs Pp 350, with 14 plates Paris Masson et Cie, 1939

This handsome monograph, beautifully illustrated, deals with all aspects of celiac disease, or idiopathic steatorrhea. In addition to a review of the literature the author presents his own experiences with conditions of this sort. While the pediatric side is emphasized, the book is of value to any one dealing with this group of diseases.

EFFECT OF LIVER THERAPY ON PATHWAYS OF SPINAL CORD IN SUBACUTE COMBINED DEGENERATION

CHARLES DAVISON, M D

NEW YORK

It is universally recognized that liver therapy produces beneficial effects when administered to patients suffering from pernicious anemia. The efficacy of this form of treatment in the improvement of the neurologic signs and symptoms in subacute combined degeneration of the spinal cord was questioned when administration of liver was first instituted as a therapeutic measure for this disorder. During the early period of its use most observers stated the belief that the improvement was limited to the subjective neurologic symptoms and that the objective signs remained unchanged. This opinion was, however, gradually changed because of the numerous reports by Richardson,¹ Ungley and Suzman,² Needles,³ Minot and Murphy,⁴ Baker, Bordley and Longcope,⁵ Strauss, Solomon, Schneider and Patek,⁶ Hyland and Fairqu-

From the Neurological Division and Neuropathological Laboratory, Montefiore Hospital

Read at the annual meeting of the American Neurological Association at NYC, N Y, June 6, 1940 and before the Section on Neurology and Psychiatry of the Academy of Medicine New York, March 1941

1 Richardson, W. Pernicious Anemia. The Results of Treatment with Liver or Its Derivatives in Sixty-Seven Cases, *New England J Med* **200** 540, 1929

2 Ungley, C C, and Suzman, M M. Subacute Combined Degeneration of the Cord. Symptomatology and Effects of Liver Therapy, *Brain* **52** 271, 1929

3 Needles, W. Neurologic Complications of Pernicious Anemia. Effects of Treatment with Liver, Preliminary Report, *Arch Neurol & Psychiat* **26** 346 (Aug) 1931

4 Minot, G R, and Murphy, W P. Treatment of Pernicious Anemia by a Special Diet, *J A M A* **87** 470 (Aug 14) 1926, A Diet Rich in Liver in the Treatment of Pernicious Anemia. Study of One Hundred and Five Cases, *ibid* **89** 759 (Sept 3) 1927

5 Baker, B M, Bordley, J, and Longcope, W T. Effect of Liver and Liver Extract upon Symptoms and Signs Referable to Nervous System in Pernicious Anemia, *Minnesota Med* **13** 815, 1930

6 Strauss, M B, Solomon, P, Schneider, A J, and Patek, A J, Jr. Subacute Combined Degeneration of the Spinal Cord in Pernicious Anemia, *J A M A* **104** 1587 (May 4) 1935

harson,⁷ and others, who demonstrated improvement in the objective neurologic signs in those patients who received adequate amounts of liver. Despite these findings, a certain amount of skepticism prevailed because it was found difficult to accept the idea that liver could in some way influence the regeneration of destroyed axis-cylinders.

In 1931 the central nervous systems from several patients having pernicious anemia with signs and symptoms of involvement of the posterior column and pyramidal tracts of the spinal cord were studied histopathologically.⁸ Seven of 17 patients received liver therapy, but not all 7 were treated adequately. In contrast to the untreated patients, whose spinal cords showed poor gliosis⁸ in the areas of destruction, the treated patients had cords which showed proliferation of the glia in the involved pathways. The myelin sheaths and axis-cylinders presented no appreciable changes from those seen in the spinal cords of untreated patients. The only other similar observation with evidence of productivity of the glia in the affected pathways has been, as far as I was able to determine, that reported by Hyland and Farquharson⁷ in 1936.

Since 1931, 69 patients having pernicious anemia with subacute combined degeneration of the spinal cord and receiving early and intensive liver therapy have been observed clinically at this institution. In most of these patients improvement in the subjective and objective neurologic signs and symptoms was greater than in members of the group observed in 1931. On 10 of these 69 patients autopsy was performed. The pathologic process in the central nervous system of these 10 patients, who were treated more adequately than those in the first group, differed extensively. As will be shown, the extent of the pathologic process in these patients was not as great and the myelin sheaths and axis-cylinders were not as extensively destroyed as in the untreated or mildly treated patients. Furthermore, in 5 of these 10 patients the degeneration, instead of involving the posterolateral tracts, was limited to the posterior columns and rarely invaded the pyramidal pathways. In the other 5 patients, although there was posterolateral involvement, the greatest pathologic changes were present in the posterior columns. In all of the 10 patients there was marked proliferation of the glia in the destroyed pathways, even more extensive than in the 7 treated patients whose cases were reported in 1931.

7 Hyland, H. H., and Farquharson, R. F. Subacute Combined Degeneration of the Spinal Cord in Pernicious Anemia. Results of Treatment in Seventy-Four Consecutive Cases with Certain Clinical Observations, *Arch Neurol & Psychiat* **36** 1166 (Dec) 1936.

8 Davison, C. Subacute Combined Degeneration of the Cord Changes Following Liver Therapy. A Histopathologic Study, *Arch Neurol & Psychiat* **26** 1195 (Dec) 1931.

MATERIAL AND METHOD

The cases of 10 patients who had pernicious anemia with neurologic signs and symptoms referable to the spinal cord and on whom autopsy was performed formed the basis of this study. All 10 patients received liver therapy, some more adequate than others (table).

Sections from the spinal cord at various levels were cut transversely and longitudinally and stained by the myelin sheath, sudan III, Holzer, Mallory phosphotungstic, Bielschowski and cresyl violet methods. Special study was made of the myelin sheaths, the axis-cylinders and the glia. These sections were carefully differentiated from sections which might have shown an ascending or descending degeneration. Comparisons were also made with the material previously studied in 1931 from untreated or inadequately treated patients.

As the histopathologic changes associated with subacute combined degeneration are well known, a detailed description of them will be omitted in this presentation. It is to be emphasized, however, that the glial reaction in cases of subacute combined degeneration without liver therapy is regressive in type—poor gliosis.

ANALYSIS OF MATERIAL

Ten patients whose cases are outlined in the table form the basis of this material. For the purpose of this study the detailed histories, physical signs and histopathologic findings in each individual case are deemed irrelevant and are therefore omitted.

Clinical Evaluation—Only a few clinical remarks will be made. A more detailed evaluation of these 10 and about 60 other cases in which the patients were observed and the improvement in the neurologic signs and symptoms will form the subject of another presentation.

The 10 patients included 3 men and 7 women. The ages varied between 35 and 76. One patient was in the fourth, 2 in the fifth, 2 in the sixth, 3 in the seventh and 2 in the eighth decade.

The duration of the illness varied from nine months to eight years, the average being about four years and four months. Only 3 patients of the group lived only two years or less after the illness began, and their ages, with periods of survival, were 63 (one year, five months), 76 (two years) and 65 (nine months), respectively.

Blood Picture and Gastric Analysis—All of the patients except patient 7 had at one time or another a blood picture typical of pernicious anemia. Patient 7 had a normal blood picture even before the liver therapy was instituted, achlorhydria, however, was noted immediately. The diagnosis of pernicious anemia was considered in this instance on the basis of the neurologic signs referable to the posterior columns and the achlorhydria. Such cases are within the experience of most physicians. All 10 patients had achlorhydria.

Clinical Neurologic Findings—All 10 patients showed signs and symptoms referable to the spinal cord. The onset of the neurologic symptoms in most instances, except cases 8 and 9, occurred some time

after the diagnosis of pernicious anemia was made. In the aforementioned 2 cases the neurologic symptoms were present at the time that a diagnosis of pernicious anemia was made.

Patients with Subacute Comb

No	Sex	Age	Duration of Illness	Blood Picture					Gastric Analysis	Duration of Clinical Neurologic Signs	Changes in the Spinal Cord
				Hemo globin, %	Red Cells	Color Index	White Cells	Differential Picture			
1	F	42	8 yr	60	4,600,000	0.65	10,450	Slight variation in size and shape of red blood cells, no nucleated red cells	Achlorhydria	4 yr	Posterolateral columns, greater involvement of posterior columns
2	F	48	3 yr	85	4,350,000	0.97	7,400	Anisocytosis, poikilocytosis	Achlorhydria	1 yr, 3 mo	Posterolateral columns, greater involvement of posterior columns
3	M	63	1 yr, 5 mo	100	3,870,000	1.30	7,600	Anisocytosis, poikilocytosis	Achlorhydria	11 mo	Posterolateral columns
4	F	57	2 yr, 3 mo	82	4,500,000	0.91	12,000	Picture typical of pernicious anemia	Achlorhydria	2 yr	Posterolateral columns
5	F	73	7 yr	Blood picture prior to liver therapy					Achlorhydria	4 yr	Posterolateral columns, right pyramidal tract more involved than left
				40	1,300,000	1.53	4,500	Picture typical of pernicious anemia			
6	M	35	7 yr	After liver therapy					Achlorhydria	1 yr, 4 mo	Posterior columns, slight involvement of right pyramidal tract
				87	4,500,000	0.96	6,800	Normal picture			
7	M	56	8 yr	Blood picture prior to liver therapy					Achlorhydria	7 yr	Posterior columns
				45	2,090,000	1.07	7,400	Picture typical of pernicious anemia			
8	F	76	2 yr	After liver therapy					Achlorhydria	2 yr	Posterior columns
				90	5,400,000	0.83	9,600	Normal picture			
9	F	65	9 mo	Blood picture prior to death					Achlorhydria	9 mo	Posterior columns, slight involvement of right pyramidal tract
				97	4,860,000	1.00	11,600	Normal picture			
10	F	67	4 yr, 6 mo	Blood picture prior to liver therapy					Achlorhydria	2 yr	Posterior columns
				72	3,260,000	1.10	5,700	Moderate anisocytosis and macrocytosis			
9	F	65	9 mo	After liver therapy					Achlorhydria	9 mo	Posterior columns, slight involvement of right pyramidal tract
				84	4,880,000	0.86	9,500	Normal picture			
10	F	67	4 yr, 6 mo	Blood picture prior to liver therapy					Achlorhydria	2 yr	Posterior columns
				45	1,860,000	1.21	4,300	Picture typical of pernicious anemia			
10	F	67	4 yr, 6 mo	One week after liver therapy					Achlorhydria	2 yr	Posterior columns
				59	3,310,000	0.89	5,600	Anisocytosis, poikilocytosis			
10	F	67	4 yr, 6 mo	Blood picture prior to liver therapy					Achlorhydria	2 yr	Posterior columns
				38	1,800,000	1.05	6,000	Picture typical of pernicious anemia			
10	F	67	4 yr, 6 mo	After liver therapy					Achlorhydria	2 yr	Posterior columns
				75	3,700,000	1.01	9,500	Anisocytosis, poikilocytosis			

Effect of Liver Therapy—The subjective neurologic symptoms improved in all cases, except that of patient 2. In the latter, the improvement could not be evaluated because the patient was observed at this institution only for twenty-four hours. Apparently this patient was not treated adequately with liver. The subjective improvement in the neurologic symptoms of patient 9 was slight. This patient was ill for only nine months and died of bronchopneumonia. Apparently she did not

receive sufficient liver therapy. Had she lived longer, improvement might have occurred. Objective improvement in the neurologic signs was observed only in patients 6, 7 and 8. In patients 7 and 8 the

degeneration Who Received Liver Therapy

Liver therapy, length of period	Improvement After Liver Therapy	Type of Glial Reaction	State of Myelin Sheaths and Axis Cylinders	Comment
2 yr, 2 mo	Subjective	Progressive, moderate gliosis, noticeable in the posterior columns	Considerable destruction	Patient received liver before admission to the hospital
3 yr		Slight gliosis in the posterior columns	Considerable destruction	Patient in the hospital only for 24 hours, previous blood counts about the same, blood picture before liver therapy unobtainable, treatment inadequate
1 yr, 5 mo	Subjective	Progressive, moderate gliosis, most noticeable in the posterior columns	Moderate destruction	
2 yr	Subjective	Progressive, appreciable gliosis in posterolateral tracts	Moderate destruction	Blood picture prior to liver therapy unobtainable
3 yr, but not regular	Subjective	Progressive, appreciable gliosis in posterior columns and right pyramidal tract	Moderate destruction	Death from coronary disease, further improvement in neurologic symptoms possible had patient lived longer
1 yr, 4 mo	Subjective, objective	Progressive, appreciable gliosis in posterior columns and right pyramidal tract	Moderate destruction	Onset at 28 years of age unusual, disappearance of mental symptoms shortly after liver therapy, death from meningitis secondary to sinusitis
8 yr	Subjective, objective	Progressive, appreciable gliosis in posterior columns	Moderate destruction of myelin sheaths, slight destruction of axis cylinders	Blood picture normal even before liver therapy, disappearance of Babinski signs after liver therapy, death from carcinoma of the tongue
1 yr, 3 mo	Subjective, objective	Progressive, appreciable gliosis in posterior columns	Moderate destruction of myelin sheaths, slight destruction of axis cylinders	Mental symptoms also present, death from myocardial disease
6 mo	Subjective, slight	Poor gliosis, status spongiosus	Considerable destruction in posterior columns	Death from bronchopneumonia, apparently insufficient liver administered, limitation of process mostly to posterior columns, possible due to short duration of illness
1 yr, 5 mo	Subjective, objective	Progressive, appreciable gliosis in posterior columns	Moderate destruction of myelin sheaths, slight destruction of axis cylinders	Death from paratyphoid fever

Babinski sign disappeared after liver therapy. In patients 6 and 8 the mental symptoms cleared up shortly after liver therapy was instituted.

Histopathologic Evaluation—In patients 1, 2, 3, 4 and 5 the histopathologic process involved the posterolateral columns of the cord as in the usual cases of subacute combined degeneration (fig 1 *A, B* and *C*) in patients moderately treated with liver. In patient 5, although the changes were present in the posterolateral columns, the right pyramidal

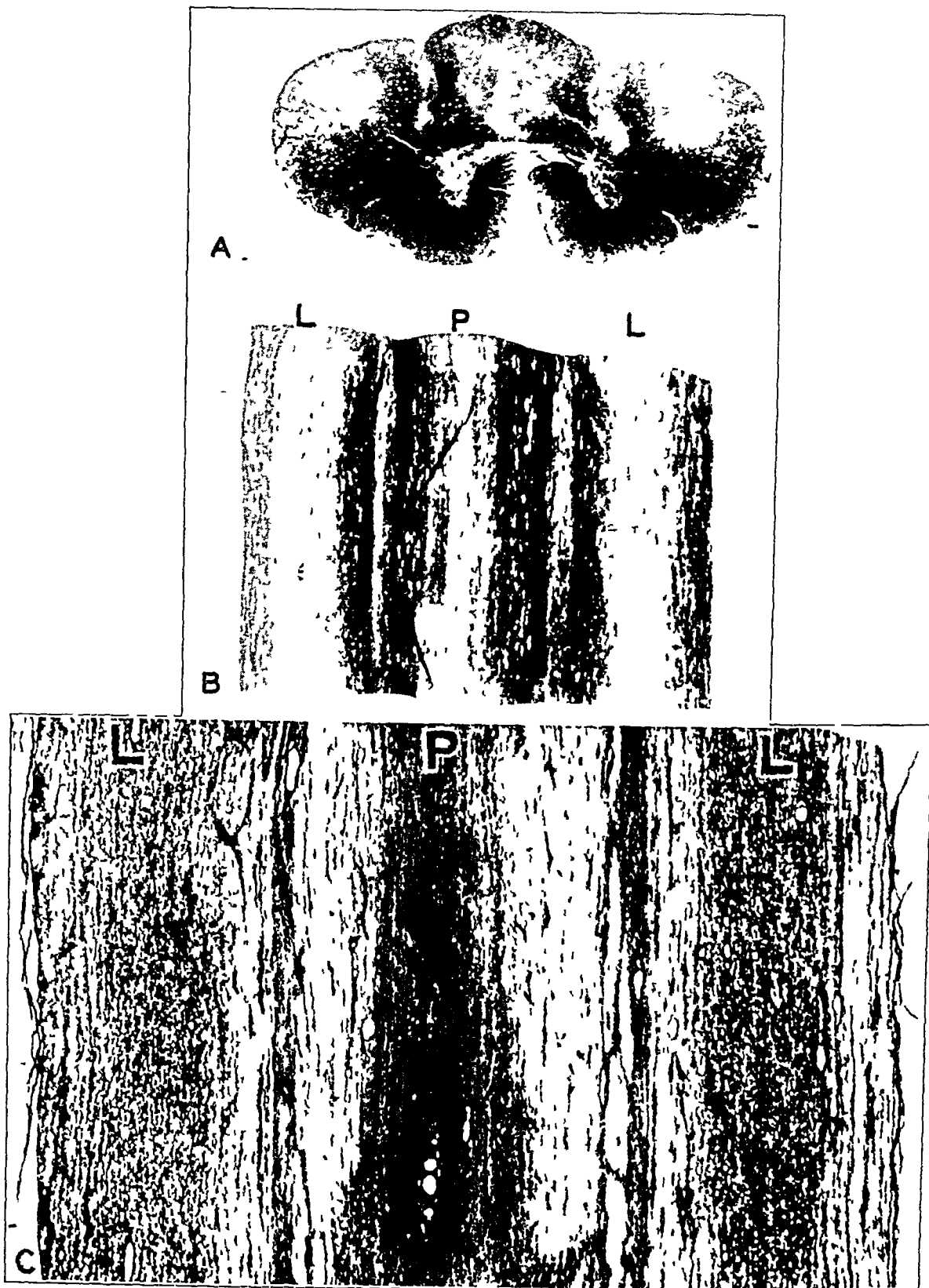


Fig 1—*A*, transverse section of the spinal cord showing involvement of the posterolateral tracts, *B*, longitudinal section of the same cord as that from which the section in *A* was taken Myelin sheath stain *C*, longitudinal section disclosing gliosis in the posterolateral tracts *L*, indicates lateral tracts, *P*, posterior columns Notice that the gliosis is most pronounced in the posterior columns The patient in this case was moderately treated Holzer stain

tract was affected more than the left (fig 2). In these 5 patients there was moderate gliosis (fig 3 *A* and *B*) in the involved pathways, as found in the previously reported cases of 7 patients who were treated with liver, the gliosis, however, was most pronounced in the posterior columns (figs 2 *C* and 3 *A*) a condition which was best noted in the longitudinal sections. The destruction of the myelin sheaths and axis-cylinders (fig 4 *A* and *B*) although not as extensive as in the untreated patients, differed little from that in the 7 treated ones just mentioned. It seemed to me, however, that the destruction of the myelin sheaths and axis-cylinders was less extensive. As it was difficult to evaluate this difference with certainty, these 5 patients are placed in the same group as the 7 whose cases were previously reported.⁵

In patients 6 and 9 the pathologic process was limited to the posterior columns and slightly to the right pyramidal tract (fig 5 *A*

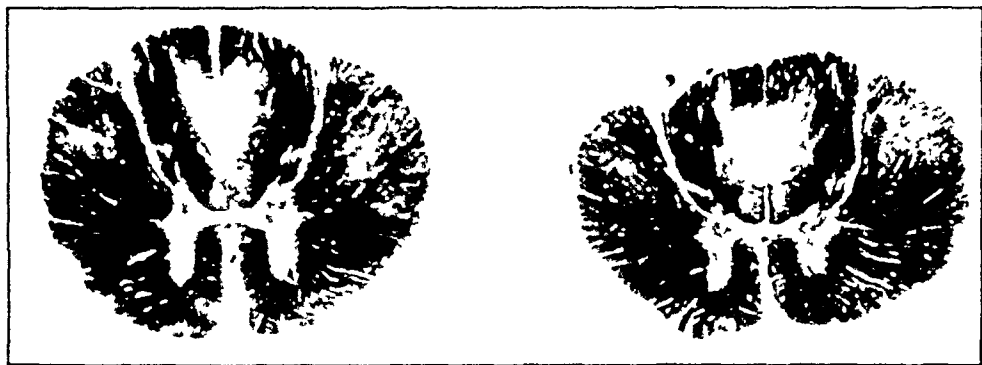


Fig 2 (case 5)—Transverse sections through the thoracic region disclosing appreciable involvement of the posterior columns and slight involvement of the pyramidal pathways, on the right more than on the left, myelin sheath stain

and *B*) Out of 17 cases⁵ of subacute combined degeneration of the spinal cord, in 10 of which the patients were not treated with liver and in 7 only partially treated with liver, there was limitation of the pathologic process to the posterior columns in only 1 instance. The patient in this case lived only for eight months after the onset of the pernicious anemia. Had he lived longer, the pathologic process most likely would have spread to the pyramidal tracts. The gliosis in patient 6 was noticeable in the posterior columns and in the right pyramidal tracts. There was moderate destruction of myelin sheaths and axis-cylinders. The onset of the illness in this patient (patient 6), at the age of 28, was unusual. The patient died at the age of 35, after meningitis secondary to sinusitis. In patient 9 there was poor gliosis (fig 6), and the myelin sheaths and axis-cylinders showed considerable destruction. The process in this patient differed little from that in the untreated ones. The duration of the illness was only nine months, the patient

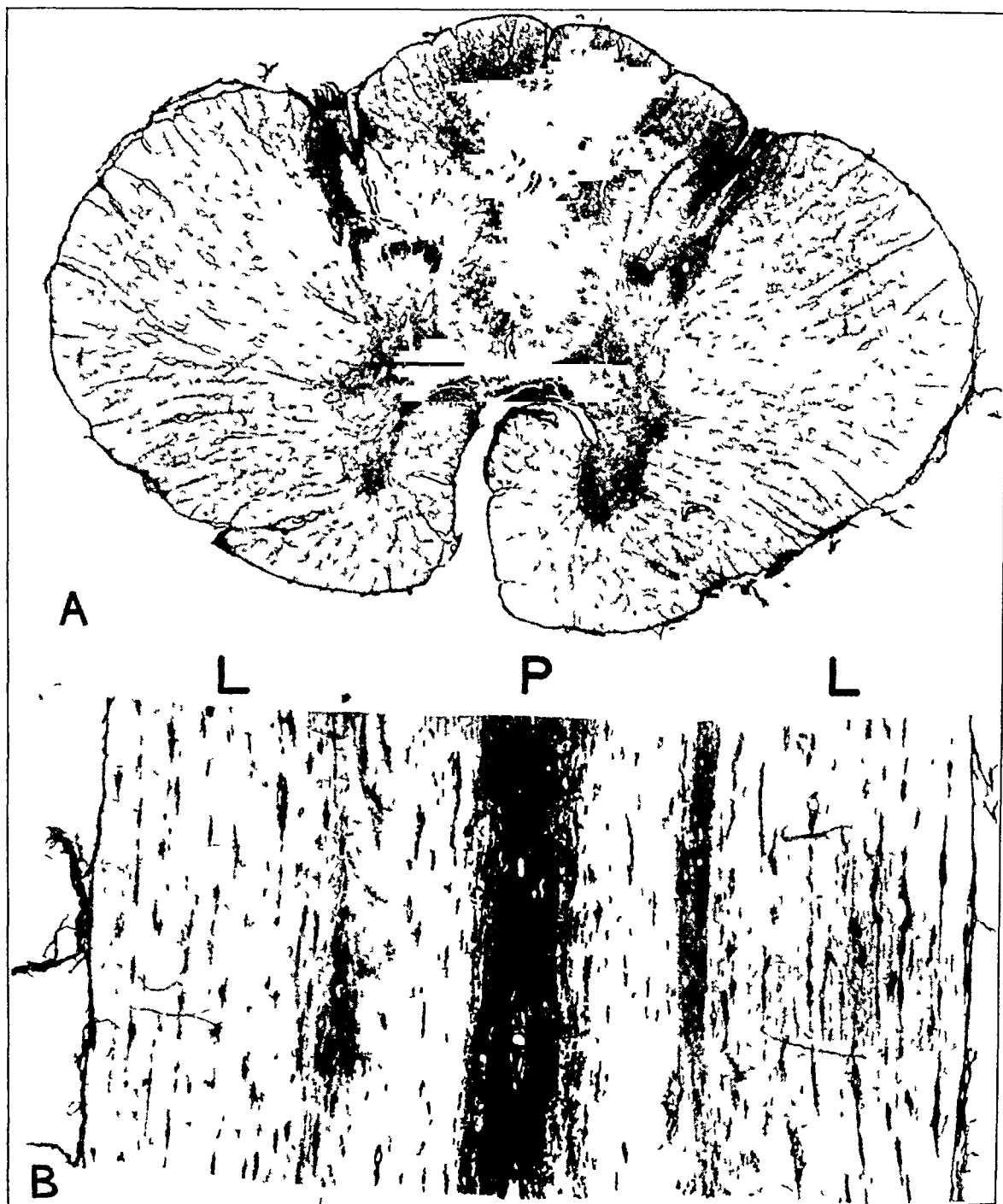


Fig 3—*A*, transverse section of the spinal cord. Notice the appreciable gliosis in the posterior columns and the moderate gliosis in the right pyramidal tract. Holzer stain. *B*, longitudinal section of the spinal cord through the posterior and lateral columns. Notice the appreciable gliosis of the posterior columns and the moderate gliosis of the right pyramidal tract. There is a small area of gliosis in the left pyramidal tract. *L*, indicates lateral tracts, *P*, posterior columns. Holzer stain.

died of bronchopneumonia. Apparently it takes a long period of liver therapy to affect the glia, i. e., to lead to glial proliferation. The short duration of the illness in the case of patient 9 possibly accounts for the

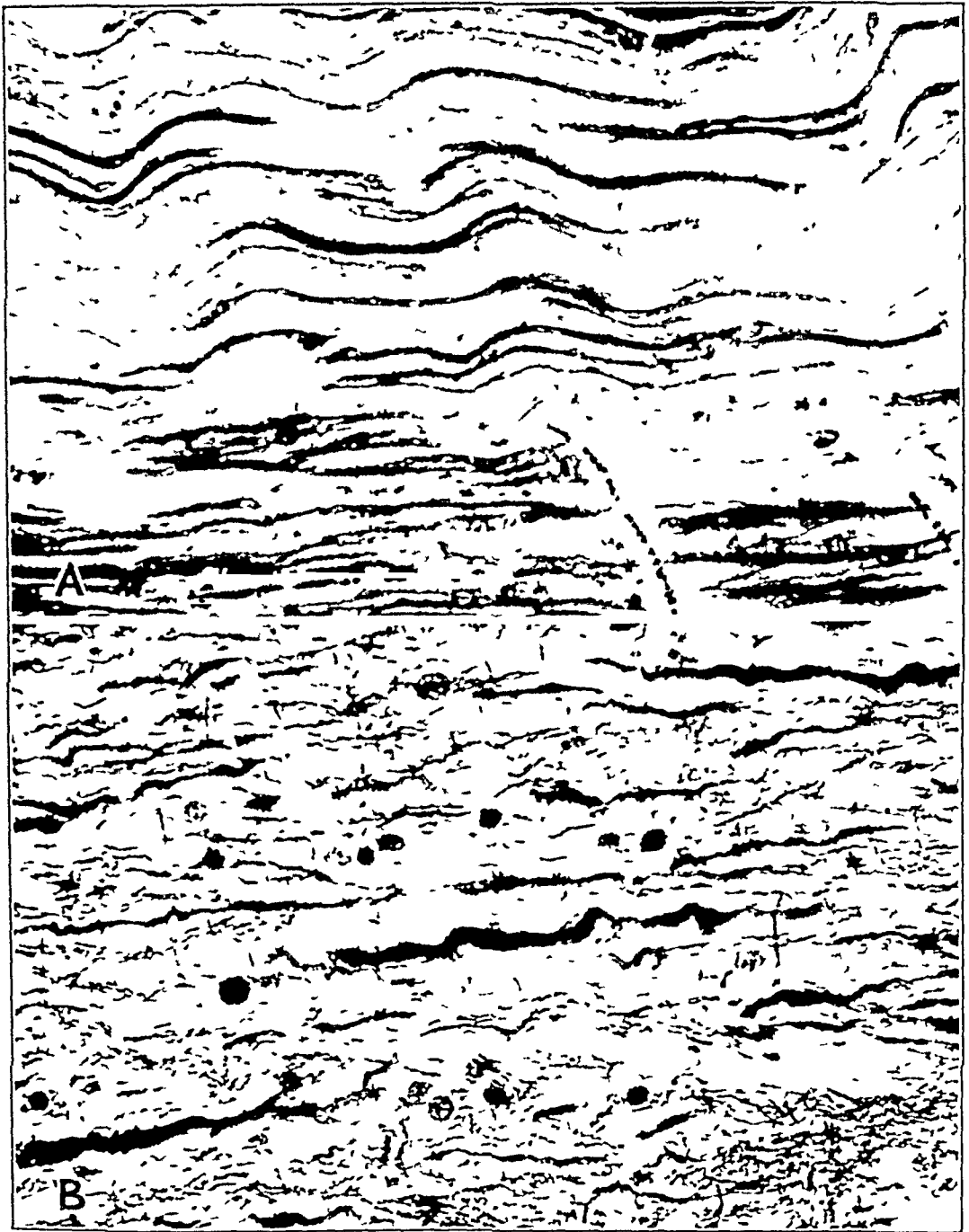


Fig 4—*A*, longitudinal section through the involved pathways showing destruction of some of the myelin sheaths. Others appear well preserved. The patient received liver therapy, but not in adequate quantities. Myelin sheath stain, $\times 154$. *B*, destruction of axis-cylinders, fragmentation, swelling and corkscrew appearance. This section is from the same patient as that shown in figure 4 *A*. Bielschowsky stain, $\times 308$.

limitation of the pathologic process to the posterior columns and the slight involvement of one pyramidal tract

In patients 7, 8 and 10 the pathologic process was limited to the posterior columns (fig 7*A* and *B*) The gliosis in these 3 patients was considerable (fig 8) and was present only in the affected pathways,

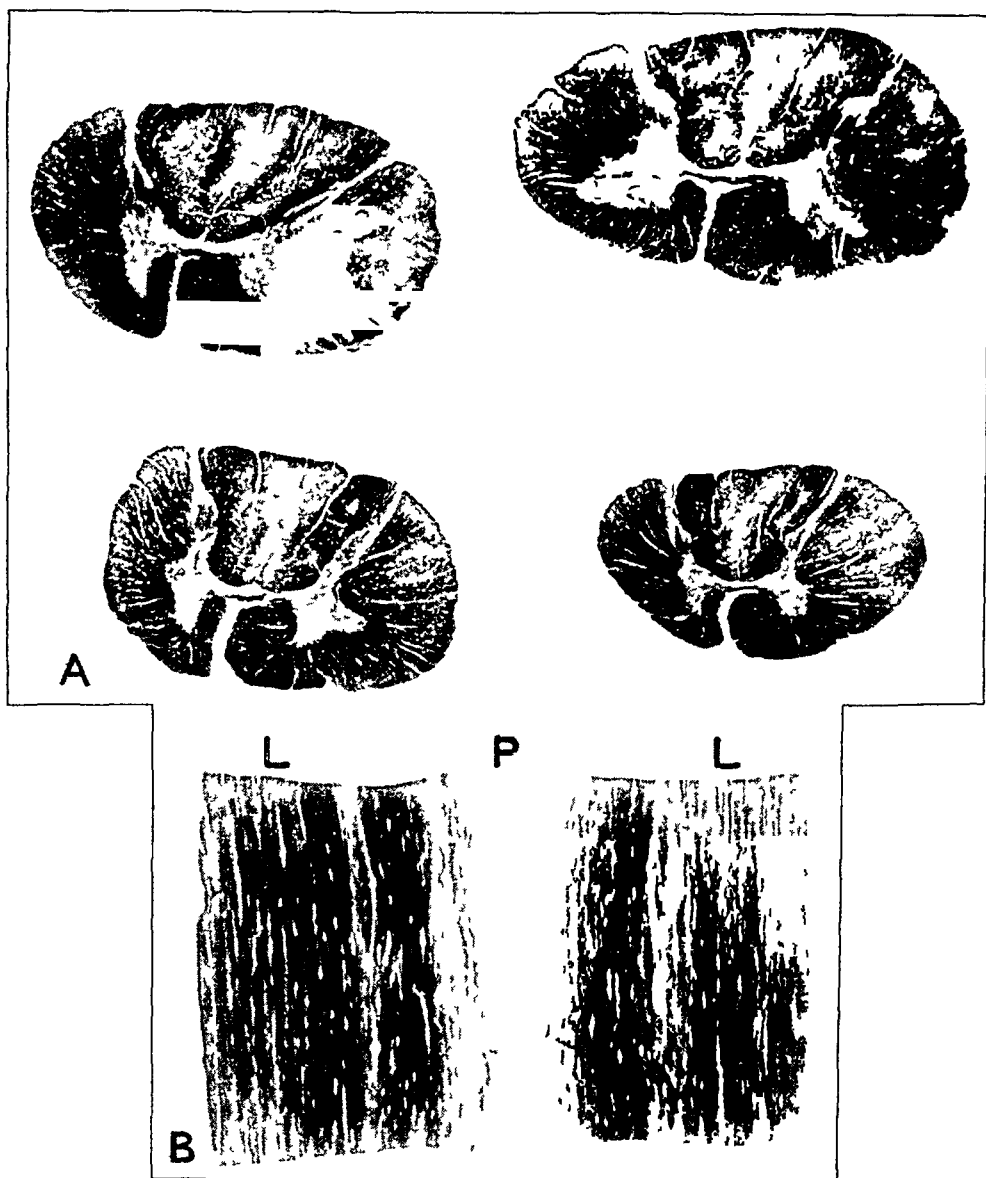


Fig 5 (case 6) —*A*, transverse sections of the spinal cord through various segments showing slight demyelination of the posterior columns and the right pyramidal tract. The patient showed improvement in objective neurologic signs. Myelin sheath stain. *B*, longitudinal section through the posterolateral columns, showing involvement of the posterior columns and right pyramidal tract. The destruction of the pyramidal tract is less extensive than that of the posterior columns. *L*, indicates lateral tracts, *P*, posterior columns. Myelin sheath stain.

that is, in the posterior columns. All these patients showed moderate destruction of the myelin sheaths and only slight destruction of the axis-cylinders (fig 9 *A* and *B*). The degree of destruction is best demonstrated when compared with that of the myelin sheaths and axis-cylinders in the less adequately treated patients (fig 4 *A* and *B*). The liver therapy was most effective in these 3 instances and led to limitation of the process to the posterior columns, appreciable gliosis, moderate destruction of the myelin sheaths (fig 9 *A*) and only slight swelling of the axis-cylinders (fig 9 *B*). In only this type of condition can one

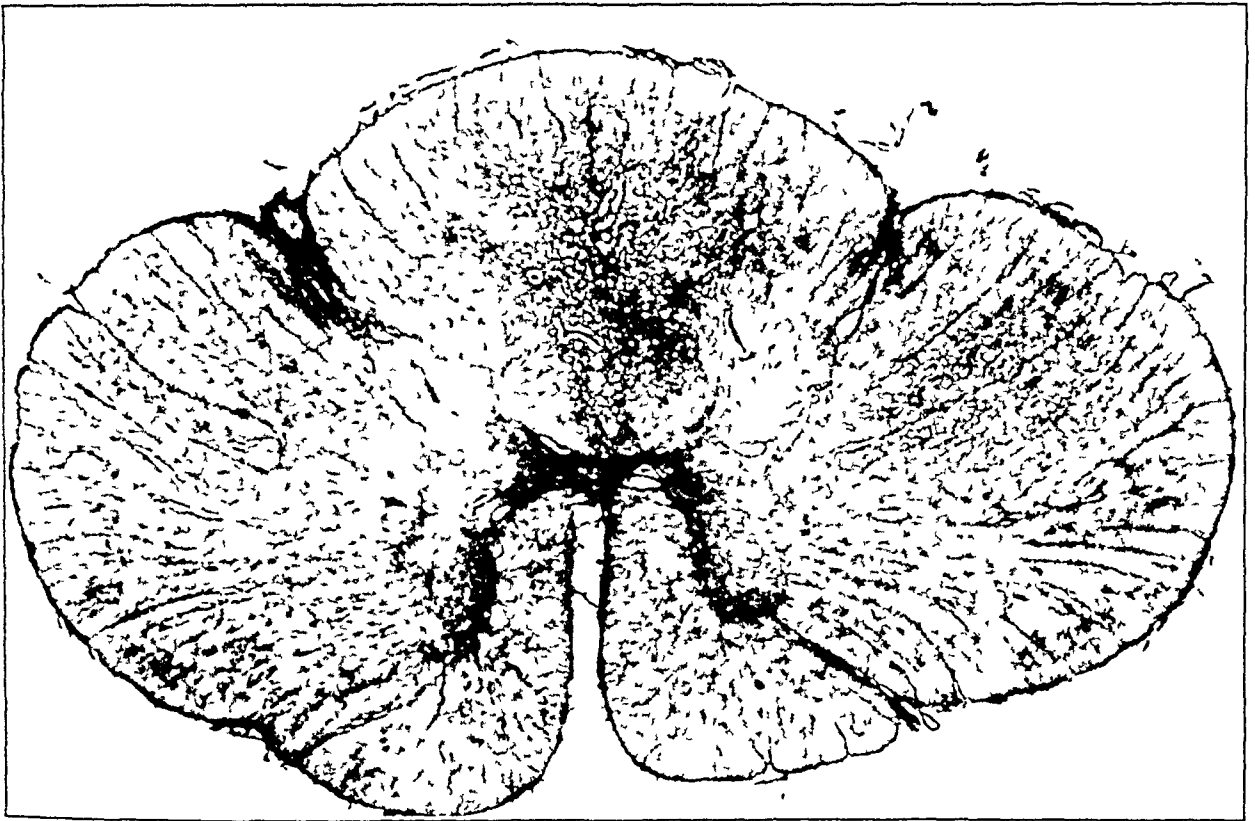


Fig 6 (case 9) —Notice the honeycomb appearance and the poor gliosis in the posterior columns and the right pyramidal tract. The left pyramidal tract also showed a slight honeycomb appearance. The patient received adequate liver therapy, but he died nine months after the onset of the illness, of bronchopneumonia. Holzer stain.

expect improvement in the objective neurologic signs. The improvement is essentially the result of only slight destruction of the axis-cylinders and the prevention of their further disintegration by the adequate administration of liver. As already indicated in a previous communication, the gliosis could not in any way restore normal function. Disease of the myelin sheaths, however, may affect the axis-cylinders and cause them to swell through irritation. The adequate administration of liver will also remove the disintegrating products and thus prevent further irritation of the axis-cylinders.

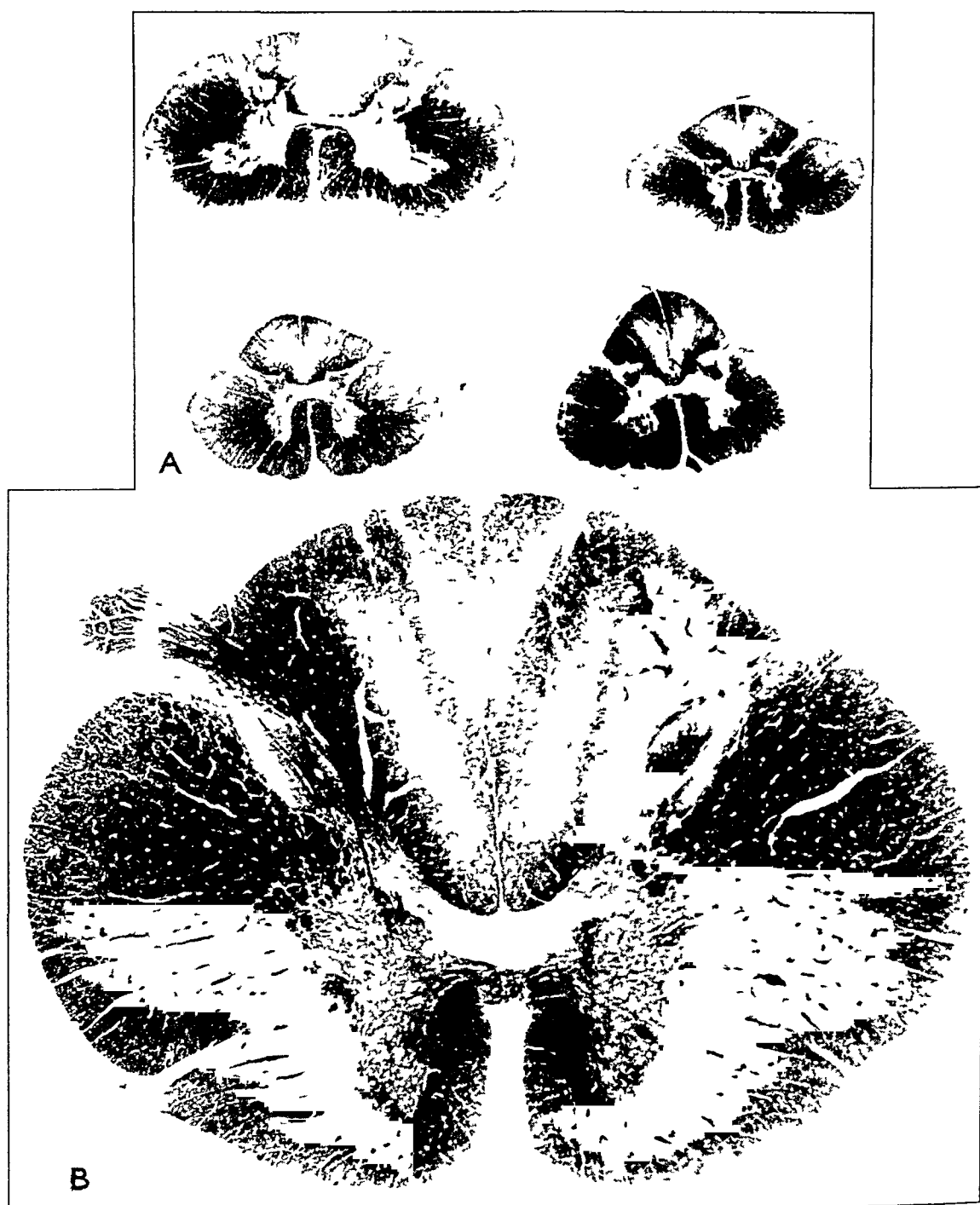


Fig 7—*A* (case 8), transverse sections of the spinal cord through various regions, showing demyelination of the posterior columns. The pyramidal pathways are spared. Myelin sheath stain. *B* (case 10), transverse section of the spinal cord showing demyelination of the posterior columns only. The pyramidal pathways are spared. Myelin sheath stain.

FACTORS INFLUENCING IMPROVEMENT IN THE NEUROLOGIC
SYMPTOMS AND CHANGES IN THE AFFECTED PATHWAYS

The improvement in the neurologic signs and symptoms, as already stressed by me in a previous communication, as well as by others, may be the result of several factors. It may be due to the amelioration of the general condition, coincident with the disappearance of the anemia, i. e., with the improved circulation. Another, and possibly the most important, factor in the improvement of the neurologic signs and symptoms is that adequate liver therapy reduces or destroys the hypothetical

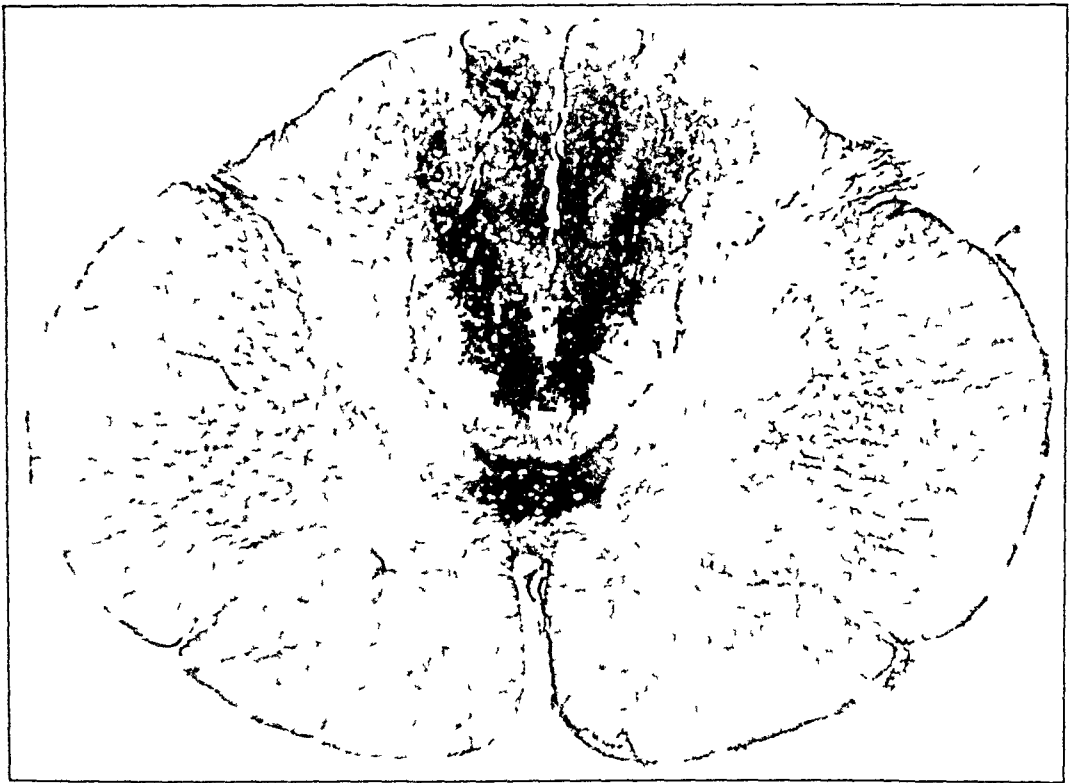


Fig 8 (case 10) —Transverse section of the spinal cord showing dense gliosis in the posterior columns. Notice that the crossed pyramidal tracts are normal. Holzer stain.

toxin that affects the myelin sheaths and axis-cylinders. From the observations in this series, it appears that the myelin sheaths are the first to be attacked. At first they become swollen, and later they disintegrate. Finally the axis-cylinders are attacked. By the early administration of liver extract, parenterally, cessation and reduction in the swelling of the myelin sheaths can be achieved. Thus further involvement or complete destruction of the axis-cylinders can be prevented. Once the axis-cylinders in the involved pathways are destroyed, their regeneration is problematic. This undoubtedly is the reason for the difference in the

improvement of the myelin sheaths and axis-cylinders (fig 9 *A* and *B*) in this series of adequately treated patients and that in the group of patients previously reported on (fig 4 *A* and *B*) who were less adequately treated

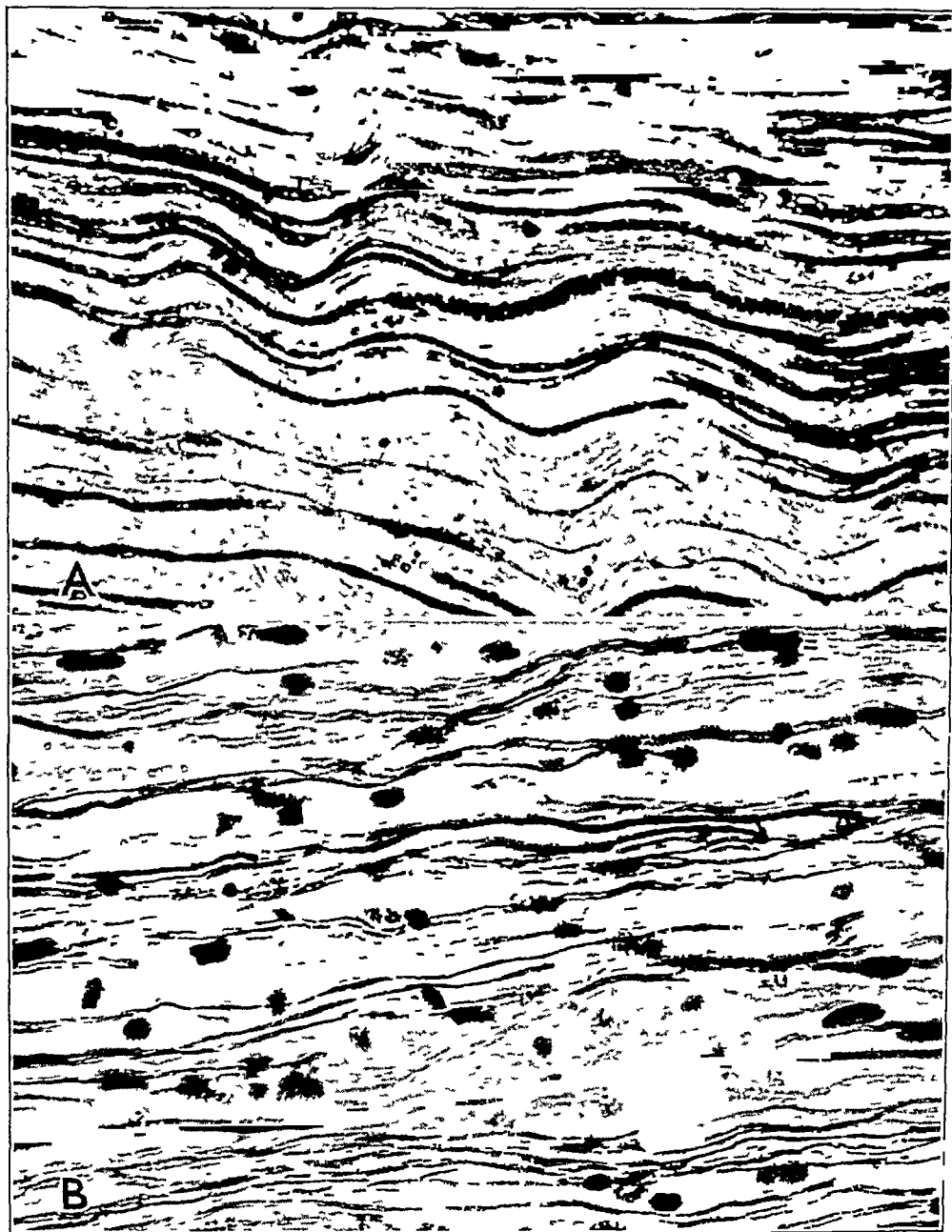


Fig 9—*A*, longitudinal section through the involved posterior columns of the cord from an adequately treated patient, showing moderate destruction of the myelin sheaths. Compare this section with that from the cord of a moderately treated patient shown in figure 4 *A*. Myelin sheath stain, $\times 154$. *B*, longitudinal section (similar to that in *A*) through the involved posterior columns showing preservation of the axis-cylinders except for occasional swelling. Compare this with the section of the cord from a moderately treated patient shown in figure 4 *B*. Bielschowsky stain, $\times 308$.

Some clinicians interested in pernicious anemia and its neurologic complications are under the impression that regeneration of the axons of the involved pathways in subacute combined degeneration of the cord may take place in a manner similar to regeneration of axons in the peripheral nerves. It is true that by the new methods of neurofibrillar study it has been demonstrated that the production of new fibers, clubs, cones and ramified axons may occur in various lesions of the spinal cord of man and animals. These findings, while they demonstrate signs of repair comparable in principle with those of the central stump of the peripheral nerves, do not contradict the conception of the impossibility of complete regeneration of axis-cylinders in the spinal cord. These later investigations have also demonstrated that after a certain length of time the restoration of the axon in the spinal cord stops, that the axon atrophies and that finally the nerve sprouts break down completely. On the basis of these findings, it can hardly be expected that destroyed axis-cylinders in the spinal cord should regenerate.

The intense gliosis or glial productivity (figs 3*B* and 8) of the involved pathways in treated patients, in contrast to the poor gliosis seen in untreated patients,⁸ is probably caused by a reduction either in the amount or in the strength of the hypothetical toxin. The limitation of the pathologic process to the posterior columns in some of these patients and the lessening of the pathologic changes in the pyramidal pathways in other patients may be explained on the same basis.

In view of these findings, it may be concluded that in cases of subacute combined degeneration there may be an improvement in the neurologic signs and symptoms provided that the myelin sheaths and axis-cylinders are not severely affected. Early administration of liver, preferably parenterally and in adequate quantities, may arrest the process in the involved myelin sheaths and axis-cylinders and may restore the function of the axis-cylinders provided they are not completely destroyed. The sooner this treatment is instituted after the onset of the neurologic signs and symptoms, the greater are the chances for these signs and symptoms to disappear. Furthermore, the early administration of adequate liver therapy not only may arrest or offset the progression of subacute combined degeneration of the cord but may also completely prevent this condition from becoming a complication of pernicious anemia, as shown by Strauss and his associates in a series of 80 cases.

SUMMARY

The cases of 10 patients who had pernicious anemia with subacute combined degeneration of the cord and who received liver therapy were studied clinically and histologically.

The subjective neurologic symptoms improved in all cases except 1. Improvement in the objective neurologic signs was observed in only 3 cases.

The pathologic process in these instances was not as noticeable and the myelin sheaths and axis-cylinders were not as extensively destroyed as in cases of untreated or mildly treated patients. In 5 of these 10 cases the degeneration, instead of involving the posterolateral tracts, was limited to the posterior columns and rarely invaded the pyramidal pathways. Even in the other 5 cases the pathologic changes were most marked in the posterior columns. In all instances there was a progressive glial change (gliosis) which was most pronounced in the posterior columns. This type of gliosis was not observed in patients with subacute combined degeneration who did not receive liver therapy.

By the early administration of adequate liver extract parenterally, cessation and reduction in the swelling of the myelin sheaths can be accomplished, thus preventing further destruction of the axis-cylinders. The function of the axis-cylinders can thus be restored, provided they are not completely destroyed. This form of treatment also induces glial productivity.

CHRONIC NONLEUKEMIC MYELOSIS

REPORT OF A CASE WITH MEGAKARYOCYTIC MYELOID SPLENOMEGALY,
LEUKOERYTHROBLASTIC ANEMIA, GENERALIZED OSTEO-
SCLEROSIS AND MYELOFIBROSIS

GURTH CARPENTER, M B, M R C P

AND

C M FLORY, M D

CHICAGO

This report concerns a case in which were presented generalized diffuse osteosclerosis generalized fibrosis of the bone marrow, an arresting erythroleukoblastic blood picture with numerous 'atypical platelets' and primitive cells with megakaryocytoid characteristics and splenomegaly characterized by myeloid metaplasia in which megakaryocytes were numerous. This case is unique in presenting the association of such advanced changes in blood and bone.

The French authors, Emil-Weil and Clerc,¹ in 1902, and Vaquez and Aubertin,² in 1904, first discussed a syndrome characterized by splenomegaly due to myeloid change and a leukemia-like blood picture, which they suggested showed clinical and pathologic differences from leukemia proper (leukemic myelosis). Since then the reports of approximately 70 cases have been contributed in which are recognized certain common characters of this polymorphic, leukemia-like syndrome. Usually there is hepatosplenomegaly due to myeloid metaplasia in which, in addition to leukoblastic cells, erythroblasts are constantly prominent and giant cells (megakaryocytes) are numerous. The blood picture displays widely varying conditions, from a late initial polycythemia to varying grades of anemia, usually normochromic but occasionally hyperchromic, nucleated red cells have been prominent in all but a few cases, and the white cell count ranges from that characteristic of leukopenia with few, or no, primitive cells to over 100,000 cells with many leukoblastic forms. Changes in the bone marrow have ranged from hyperplasia to hypoplasia with intense fibrosis and sclerosis of bone. The principal features which have been held to differentiate this syndrome

From the Douglas Smith Foundation in the Department of Medicine, and the Department of Pathology, the University of Chicago

1 Emil-Weil, P, and Clerc, A. La splénomégalie chronique avec anémie et réaction myéloïde du sang, *Semaine med* 22 373, 1902

2 Vaquez and Aubertin. Nature de l'anémie splénique myeloïde, *Compt rend Soc de biol* 56 792, 1904

from leukemic myelosis (myelogenous leukemia) are the diversity of cell types in metaplastic organs and in the bone marrow, the commonly low white cell count with the low proportion of circulating primitive cells and the almost constant presence of nucleated red cells, the frequency with which osteosclerosis and myelosclerosis are encountered and the absence of characteristic leukemic infiltrations

These various arresting characteristics have led to the reporting of cases under a wide variety of names, such as myeloid splenic anemia (Vaquez and Aubeitin,² 1904), atypical myeloid leukemia (Hirschfeld,³ 1905), aleukemic myelosis (Hirschfeld,⁴ 1914), osteosclerotic pseudo-leukemia (Pastore,⁵ 1922, Wolf,⁶ 1932), chronic nonleukemic myelosis (Mavros,⁷ 1931, Hickling,⁸ 1937), megakaryocytic myeloid splenomegaly (Emil-Weil and associates,⁹ 1933 and later), myelosclerosis (Vaughan,¹⁰ 1936) and leukoerythroblastosis (McMichael and McNee,¹¹ 1936)

We realize that secondary myeloid metaplasias and leukoerythroblastic anemias which accompany the destruction of bone marrow may also be termed nonleukemic myelosis, but we are not here concerned with the manifestly symptomatic metaplasias, and hereafter for the purposes of this paper we shall use the name "nonleukemic myelosis" to designate specifically the aforementioned syndrome. The full discussion of its wide ramifications would make a more extensive paper than is in order here, reference should be made to the communications of Hickling,⁸ of Vaughan and Harrison¹² and of Downey and Nordland¹³

3 Hirschfeld, H. Ueber atypische Myeloidwucherung, *Folia haemat* **2** 665 1905

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5 Pastore, S. Pseudoleukemia e osteosclerosi, *Policlinico* **29** 595, 1922

6 Wolf, C. Ueber einen Fall von osteosklerotischer Pseudoleukemie, *Beitr z path Anat u z allg Path* **89** 151, 1932

7 Mavros, A. Aleukamische, besser nichtleukamische, Myelose mit Osteosklerose, *Folia haemat* **43** 323, 1931

8 Hickling, R. A. Chronic Non-Leukemic Myelosis, *Quart J Med* **6** 253, 1937

9 Emil-Weil, P., Chevalier, P., and See, G. Splénomégalie myéloïde megacaryocytaire amyelocytémique, *Sang* **7** 773, 1933

10 Vaughan, J. N. Leuco-Erythroblastic Anemia, *J Path & Bact* **42** 541, 1936

11 McMichael, J., and McNee, J. W. Leuco-Erythroblastosis, *Edinburgh M J* **43** 303, 1936

12 Vaughan, J. M., and Harrison, C. V. Leuco-Erythroblastic Anaemia and Myelosclerosis, *J Path & Bact* **48** 339, 1939

13 Downey, H., and Nordland, M. Myeloid Megakaryocytic Hepato-Splenomegaly, *Folia haemat* **62** 1, 1939

REPORT OF CASE

Protocol—A S., a 33 year old Swedish-American man, employed as clerk, was admitted Sept 9, 1936 to the Albert Merritt Billings Hospital of the University of Chicago

He had had a healthy childhood and adolescence. He had lobar pneumonia at the age of 21, at 25 he was told he had albuminuria and "bad kidneys," but he had never received treatment for this condition. There was no knowledge of exposure to benzene or fluorides or use of aminopyrine or of gold salts.

A sister who died of pulmonary tuberculosis was in contact with the patient in his childhood. The family history was otherwise not significant.

In March 1936 the patient noticed dull, aching pains in the back, arms and legs, which he dismissed as rheumatism. He began to experience a feeling of weight in the abdomen after meals, and constipation became severe. The abdomen began to protrude, and there was intermittent pain in the left upper quadrant. By September 1936, when he entered the hospital, he had lost 25 pounds (11.3 Kg.) in weight. He had a noticeable general pallor and was in a moderate state of subnutrition. The abdomen was extremely protuberant, and a large mass, identified as the spleen lay in the left hypochondrium, reaching the umbilicus. There was slight rubbery enlargement of the inguinal lymph nodes, but no other nodes were palpable. Extreme tenderness of the sternum was noticed on pressure, but there was no tenderness of other bones. Other findings were within normal limits.

The blood counts during the course of the illness are recorded in the table. In November 1936 the spleen was removed. In the year following splenectomy a leukemoid blood picture developed. Between 1936 and his death in 1939 the patient was admitted to the hospital seven times, each time with low grade fever and each time complaining bitterly of pain in the limbs, which he spoke of as "rheumatism." Throughout 1938 and 1939 progressive enlargement of the liver was noted. In these years there were many episodes of epistaxis and bleeding from the gums and some petechial hemorrhage. At the patient's terminal admission to the hospital his condition was marked by high fever associated with tachycardia and by dyspnea. Cough, cyanosis and production of sputum were not noticed. At various times liver, iron, arsenic and vitamin preparations were administered without apparent effect. In all, twenty-two blood transfusions were given. A single course of high voltage roentgen therapy, with a total dose of 600 r, was given over the spleen shortly before its removal.

Laboratory data are as follows. The urine in 1936 was clear, in 1938 and 1939 it showed a moderate amount of albumin and contained granular and hyaline casts. The serum agglutination tests in 1936 gave negative results for the typhoid, dysentery and brucella groups. The sedimentation rate in 1936 and 1939 was extremely rapid (uncorrected). The roentgenograms in 1936 showed normal long bones, in 1939, six months before his death, they showed the long bones to be essentially normal, but with irregular and coarse trabecular patterns at the lower end of the femur and the upper end of the tibia. The fragility of red cells in 1936, 1937 and 1939 was within normal limits (determined by Sanford's method). Sternal puncture was attempted four times between 1936 and his death in 1939, and on each occasion the results were "unsatisfactory," for reasons not stated but probably connected with the unsuspected osteosclerosis. No chemical studies of the blood were made.

Death occurred on July 22, 1939. The primary clinical diagnosis was myeloblastic-megakaryoblastic leukemia, and the secondary diagnosis, myelophthisic anemia.

*Data from Blood Counts **

Date	Hemo globin, gms per 100 cc †	Red Blood Cells	White Blood Cells ‡	Poly morpho nucleus, Neutro phils	Meta myelo phils	Myelo blasts	Lym pho cytes, Small	Lym pho cytes, Large	Mono cytes	Mega karyo cytes, Small	Plo megi karyo cytes	MCD karyo blasts	Poly morpho nucleus Eosino phils	DeGen erated Cells	Uniden tified Pumi tive Cells	Nucleated Red Cells per 100 White Blood Cells	Comment
9/8/36	7.5	2,430,000	3,100	57.0	5.0	4.0	1.0	3.5	6.5	4.5	1.0	0	0.5	0.5	0.5	9.0	Polychromasia, slight anisocytosis, few large atypical platelets, reticulocytes 8.0%, fragility normal
10/9/36		Splenectomy															
10/10/36	8.0	2,780,000	9,800	67.0	3.5	1.0	0.5	4.0	3.0	1.0	0.5	0	0	1.0	0.5	26.0	Polychromasia, anisocytosis with few macrocytes, more large and also atypical platelets
10/12/36	11.6	3,540,000	7,300	72.0	2.0	3.0	0	2.0	5.0	1.0	0	0	0	8.0	0	11.0	Anisocytosis, poikilocytosis, polychromasia, platelets 280,000
9/27/37	8.2	2,210,000	15,700	19.5	8.5	9.5	5.0	2.5	13.5	2.0	6.0	3.5	0	21.0	2.0	53.0	Great numbers of large platelets and irregular protoplasmic masses anisocytosis and poikilocytosis marked, many macrocytes
10/1/37	8.7	2,550,000	24,380	31.0	8.0	3.5	4.0	1.0	12.0	1.5	9.5	3.0	0	16.0	1.0	47.0	Platelet masses as previously red cells as previously
3/1/38	7.2	2,290,000	36,300	7.5	6.0	0.5	5.0	6.5	5.0	1.0	1.0	3.5	0	19.0	1.0	41.5	Platelet masses as previously red cells as previously, many degenerate cells with nuclei similar to small megakaryocytes others polymorphonuclear
11/25/38	8.3	2,300,000	49,000	13.5	6.5	3.0	9.0	1.0	8.0	1.5	11.0	1.5	0	10.0	0	25.0	Slight anisocytosis, few macrocytes, platelet masses as previously
1/5/39	9.5	2,370,000	86,100	10.5	6.5	11.0	8.0	3.0	10.0	0.5	6.5	1.5	0.5	11.0	1.0	43.0	Platelet masses most numerous, occasional lobulated megakaryocytic nucleus
7/11/39	5.6	1,390,000	43,000	47.5	8.5	8.0	0	3.5	8.0	1.0	1.5	1.0	0	11.5	0	1.5	Extreme reduction in platelet numbers
7/21/39	3.5	1,160,000	2,600	52.0	1.0	5.0	1.0	20.0	0	0	0	0	0	1.0	0	7.0	Atypical platelets few extreme toxicity of polymorphonuclears

* The counts presented were selected as representative from more than fifty observations
† The hemoglobin was determined by Newcomer's method
‡ Corrected for nucleated red cells

Blood Picture—The progress of the peripheral blood picture was followed through three years and fell into three phases (1) the leukopenic phase, occurring before splenectomy, (2) the leukemoid phase, occurring after splenectomy, and (3) the terminal "aplastic" phase

Characteristic counts are recorded in the table appended Till the advent of the "aplastic" phase the red cell count remained fairly constantly in the region



Fig 1—Sternum, $\times 30$, Mallory's connective tissue stain The trabeculae are numerous and dense The marrow cavity is filled with fibrous tissue

of 2,500,000, with normochromic cells Polychromasia, anisocytosis and occasional poikilocytosis were present throughout the illness Occasional macrocytes were seen during all phases The predominant nucleated red cell was the normochromic normoblast, but polychromatic normoblasts and macronormoblasts were not rare At varying times, individual erythroblasts of every degree of immaturity were encountered

The small adult megakaryocyte of the Dominici type was present from the very earliest stages of the disease. It appeared in films early in the course as a dense, pyknotic nucleus, often ovoid, surrounded by adherent and partially detached typical platelets. Frequently such nuclei were seen entirely devoid of cytoplasm, and in the differential counts these have been recorded among "degenerate cells." These small adult megakaryocytes increased considerably in the days immediately following splenectomy and remained prominent even in the "aplastic" phase. In the leukemoid phase typical myeloblasts increased greatly in proportion, as did their typical granular derivation forms (myelocytes and promyelocytes were grouped together in the counts).

A considerable proportion of cells with typical myeloblastic nuclei had atypical protoplasm. This took the form of "ameboid" extensions from the periphery of the cell, of such nature as to lead to the conclusion that they were one of the sources of "atypical platelets." The cytoplasm of some such cells with typically myeloblastic nuclei showed division into an inner zone of foamy material and an outer zone of clear protoplasm, an arrangement suggestive of the chromoplasm and hyalomere of the typical platelet.

Of the greatest interest were the precursory forms of megakaryocytes, the megakaryoblasts and the promegakaryocytes. These were identified as such in accordance with the descriptions of Downey and Nordland¹³. Metamorphic forms made apparent the derivation of the megakaryoblast from the myeloblast. The megakaryoblast had in general the same structure as the myeloblast, but the nucleus was considerably more acidophilic, the nuclear membrane more defined and the chromatin arranged in definite strands with a reticulate pattern, rather than in the diffusely stippled manner of the myeloblast, the cytoplasm was distinctly more basophilic than that of the myeloblast. Occasionally, small ameboid projections radiated from the cell margin, but generally the cytoplasm of these cells was not abnormal. The nucleus of the promegakaryocyte had greater aggregations of chromatin into spheroid or ellipsoid masses interconnected with strands than the megakaryoblast had, and the chromatin was much denser. One or more elliptic nucleoli might be present, but were frequently obscured in the mass of chromatin. The cytoplasm of these cells varied greatly. Occasionally it was represented by a diffuse, slightly foamy plasma, which might or might not contain a few azurophilic granules. Frequently it was zoned into an outer clear plasma and an inner foamy area in which azurophilic granules suggestive of Schridde's granules were present in varying numbers. From these cells many protoplasmic masses with the same varied structure as the "atypical platelets" were evidently in various stages of detachment.

It was clear that the myeloblast-megakaryoblast-promegakaryocyte series of cells was the sole source of the extraordinary numbers of atypical platelets and that small megakaryocytes gave origin to the great numbers of typical platelets. As seen in the plates, the great numbers of "atypical platelets" in the blood smears were arresting. Their size and refractory qualities made white cell counts difficult. The justification for the term "atypical platelets" lay in the fact that such bodies were seen to be derived only from the series precursory to megakaryocytes and never from cells established in the granular cell or the lymphocyte series. All the forms of abnormal platelets described at length by Downey and Nordland in their case were here reproduced, in somewhat greater numbers. They fell largely into three types: (1) platelets with a mass of clear cytoplasm ranging in size up to that of the myeloblast, (2) platelets with a mass of similar variant size with clear peripheral cytoplasm (hyalomere) and foamy central plasma

(chromoplasm) which for the most part was agranular, but which occasionally showed multiple small granules of the Schridde type and (3) platelets of typical structure but giant size, often with irregular, extended forms. Types 1 and 2 were frequently vacuolated. Rarely, a platelet mass of type 2 contained a delicate ring structure, which suggested the appearance of a retained nuclear membrane.

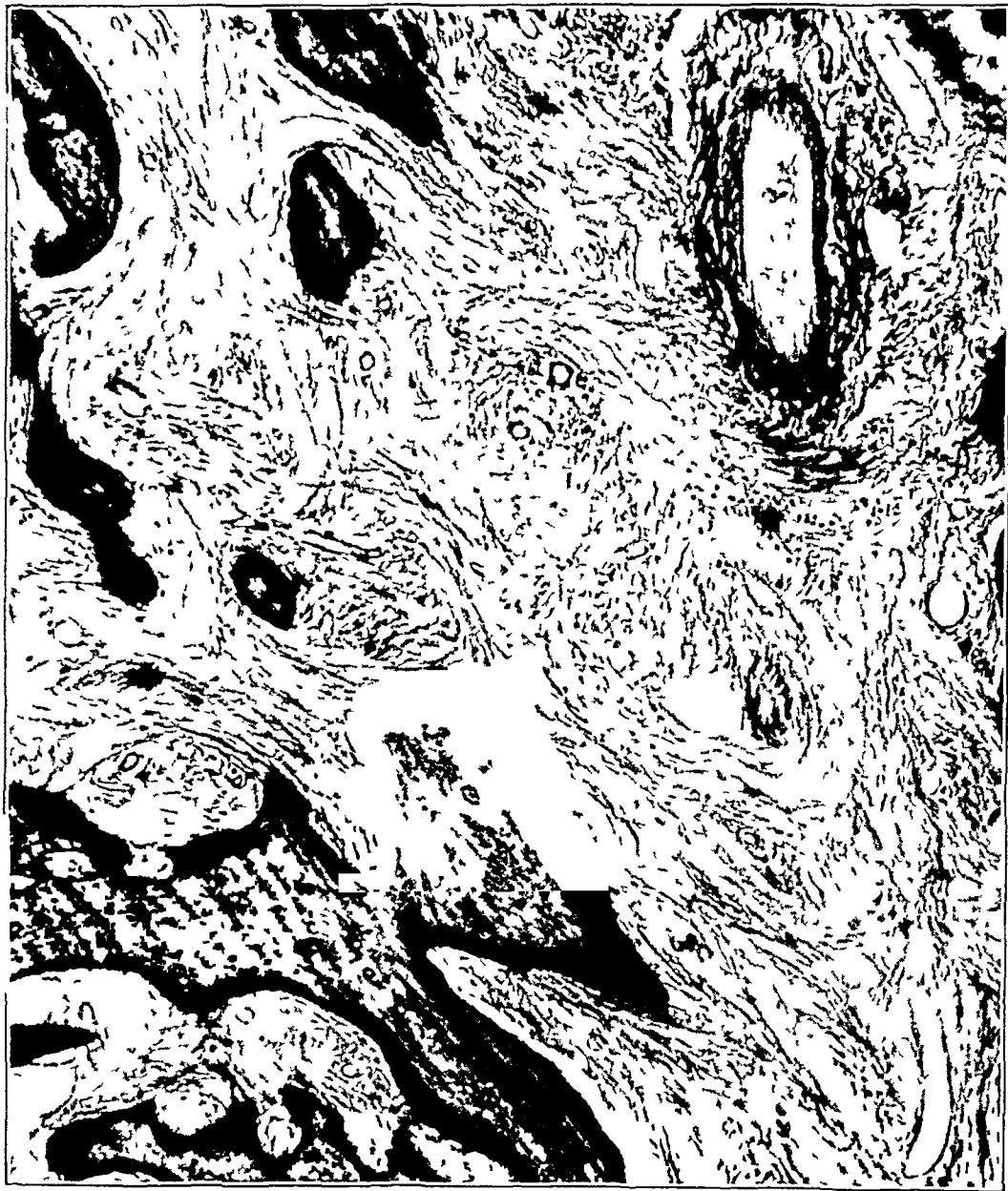


Fig 2—Lumbar vertebra, $\times 135$, Mallory's connective tissue stain. The marrow spaces are filled with fibrous tissue. Near the vein with a normal wall a few myeloid cells are seen.

within a degenerating cell but remained unexplained. A few abnormal platelets were present before splenectomy, but they increased greatly immediately thereafter. In the terminal "aplastic" phase they largely disappeared.

The Spleen—The study of this organ was made on the specimen removed surgically. A description of this organ at the time of removal was not available.

Advanced changes had occurred in the specimen which had been preserved in Kaiserling's solution. The estimated weight was 3,000 Gm. Sections embedded in paraffin were stained with hematoxylin and eosin, Mallory's connective tissue stain, the hematoxylin-eosin-azure stain, Giemsa's stain and also with stains specific for reticulum and for iron. Smears taken from the cut surface of the spleen at the time of operation and stained with Wright's stain were also available.

The splenic capsule was normal and the trabeculae few. The connective tissue showed a normal amount of reticulum and collagen. There were no areas of hemorrhage or fibrosis. The blood vessels were normal. The malpighian corpuscles were far apart. They were normal in size and cellular content. Highly cellular red pulp comprised nearly the entire splenic mass. The majority of the cells were myeloid in type. All stages of erythropoiesis were seen, with abundant normoblasts. Eosinophilic myelocytes and metamyelocytes were prominent. Many neutrophilic myelocytes were also seen. In the cords of Billroth, and less commonly in the sinusoids, were huge cells with polymorphous, multilobulate nuclei having a high content of chromatin. These were typical megakaryocytes as found in bone marrow. Attempts to stain granules in these cells were not successful. Several such cells were present in most low power fields. Many smaller cells with simple nuclei but with megakaryocytic characteristics were also identified. No evidence could be obtained from the sections as to the derivation of these large cells. The splenic sinusoids were dilated. The cells lining their walls were cuboidal and often lay free in the sinusoids. Many sinusoids contained myelopoietic cells. Some splenic macrophagocytes had taken up iron. No erythrophagocytosis was seen.

In the smears taken at the time of operation from the cut splenic surface and stained with Wright's stain, all stages of erythroblasts were seen. Myeloblasts were extremely numerous. Granular derivation forms of every type were also numerous. Eosinophilic granulocytes were not as prominent as in the sections. Lobulate megakaryocytes of the type found in bone marrow were common. Extremely numerous was the small adult type of megakaryocyte with ovoid or spheroid nuclei. Frequently, two or three such nuclei were seen embedded in a mass of platelets. Here, as in the peripheral blood, it was easy to discern megakaryoblasts and promegakaryocytes and to follow their derivation from the myeloblasts. Vast numbers of typical platelets were seen, and there were also many protoplasmic masses of the same nature as those in the blood smears. It was not possible to state that these masses were derived from any one type of cell.

Necropsy Observations—Autopsy was performed three hours after death. The body was moderately emaciated. Pallor was generalized, and the skin was slightly yellowish. A well healed splenectomy scar was the only external abnormality. Thorax. The pleural cavities contained a few fibrous and fibrinous adhesions. The right lung weighed 990 Gm and the left 960 Gm. Densely and uniformly scattered throughout both lungs were hard, grayish nodules, 1 mm in diameter. The heart was normal. The great and medium vessels showed a minimum amount of sclerosis. Abdomen. The liver extended 12 cm below the costal margin. It weighed 4,400 Gm. The triads were grayish white and prominent. The hepatic tissue about the central vein was deep brown. The gallbladder, bile ducts and pancreas were normal. No accessory spleen was found. The gastrointestinal tract was normal except for marked fibrosis of the appendix. The left kidney weighed 270 Gm and the right 290 Gm, both showed moderate cloudy swelling. The ureters and bladder and the prostate gland were normal.

Endocrine Glands. The thyroid was normal. One parathyroid was seen, which had the usual appearance, the others were not found. The thymus was atrophied. The adrenal glands were poor in lipoids but showed no other gross abnormality. The testes were normal.

Lymph Nodes In the cervical region were a few firm lymph nodes, 0.5 cm in diameter. Each axillary and inguinal region contained one or two firm, discrete nodes, 2 by 1 by 1 cm, displaying firm white tissue when cut. The tracheo-bronchial lymph nodes were slightly enlarged, but their cut surfaces were wet



Fig 3—Spleen $\times 1075$. Maximow's hematoxylin-eosin-azure stain. Lying in a cord of Billroth are discernible three megakaryocytes with multilobulate nuclei (1) and two similar cells with simple spheroidal nuclei (2). Groups of erythroblasts (3) and myeloid cells (4) are distinguished.

and anthracotic. Nodes in the porta hepatis and the peripancreatic nodes were slightly enlarged and contained areas of firm white tissue.

Skeleton The sternum, ribs, vertebrae and left midfemur were externally normal. In the short bones the cortex was of normal appearance, but the trabeculae were much denser than normal and the marrow spaces, thereby much reduced,

were filled with firm white tissue. The cortex of the femur appeared normal, but the central cavity was completely filled in by many trabeculae and the marrow replaced by firm white tissue. The bones were not more extensively examined, as the full significance of these changes was not immediately recognized.

Histologic Observations—The bone marrow, lymph nodes and liver were fixed in a mixture of solution of formaldehyde U S P and Zenker solution, and other tissues, separately in Zenker's solution and in solution of formaldehyde U S P. All the tissues were embedded in pyroxylin and stained with hematoxylin and eosin. Sections of the bone marrow were stained with Maximow's hematoxylin-eosin-azure stain, Mallory's connective tissue stain, a stain specific for iron and Foot's reticulum stain. Ziehl-Neelsen's acid-fast stain was used for the tubercle bacilli.

Bone Marrow Sections were made from the sternum, the ribs, the lumbar vertebrae and the medulla of the left midfemur. The periosteum and the cortex of the sternum, the ribs and the vertebrae were of normal thickness. The cortex of the femur appeared grossly normal but was not preserved for sectioning. The trabeculation of the marrow cavities was heavy. This was most distinct in the ribs, where more than two thirds of the marrow spaces were replaced by bony trabeculae. In the marrow of the sternum and of the lumbar vertebrae the trabeculae were much denser than normal. Trabeculation in the marrow of the left midfemur was least dense, but still many trabeculae were displayed. In all these bones some new bone was forming about the trabeculae and in the marrow cavities. No osteoclasts were seen. No normal marrow was seen. In all the spaces of the marrow was a fibrous tissue, composed largely of fine, densely packed strands of collagen, which stretched directly from one trabecula to the next, attaching itself directly to the new bone surrounding the trabeculae. In this fibrous tissue were a few strands of reticulum. The blood vessels were normal in size and number. In the marrow of the ribs and the lumbar vertebrae there were no fat cells, in the marrow of the sternum a few were present. In the marrow of the femur fat cells had the appearance of being replaced by new fibrous tissue and trabeculae. In all the bones examined, myeloid tissue was rarely seen in a low power field. In each section examined there were one or two extremely small areas in which foci of myeloid cells remained, lying between the strands of connective tissue. In these areas were many erythroblasts, many eosinophilic myelocytes and metamyelocytes, many neutrophilic myelocytes and metamyelocytes, a few megakaryocytes and a few cells with basophilic cytoplasm and a large nucleus having the appearance of myeloblasts. In a section of the marrow of the femur a small tubercle was seen.

Thus, the dominant features of the bones were (1) increased trabeculation with the apposition of new bone (osteosclerosis), (2) fibrosis of the bone marrow (myelofibrosis) and (3) intense hypoplasia of the myeloid tissue.

Lymph Nodes The enlarged axillary lymph nodes showed large areas of caseonodular tuberculosis, in which a few acid-fast bacilli could be found. The peritracheal and the peribronchial nodes were hyperplastic. In their sinuses were macrophages, a few polymorphonuclears and a few multinucleated giant cells. These giant cells resembled megakaryocytes, but they may conceivably have been atypical giant cells of tuberculosis. The abdominal lymph nodes were slightly enlarged and contained a few miliary tubercles. Elsewhere in these nodes were a few polymorphonuclears, a few eosinophilic leukocytes and a few nucleated red cells. No other lymph nodes showed any evidence of myelopoiesis.

Lungs and Bronchi Throughout the lungs was widespread miliary tuberculosis accompanied by early caseation, many acid-fast bacilli were present in the tubercles. The general cellular reaction was poor. No megakaryocytes, or fragments of

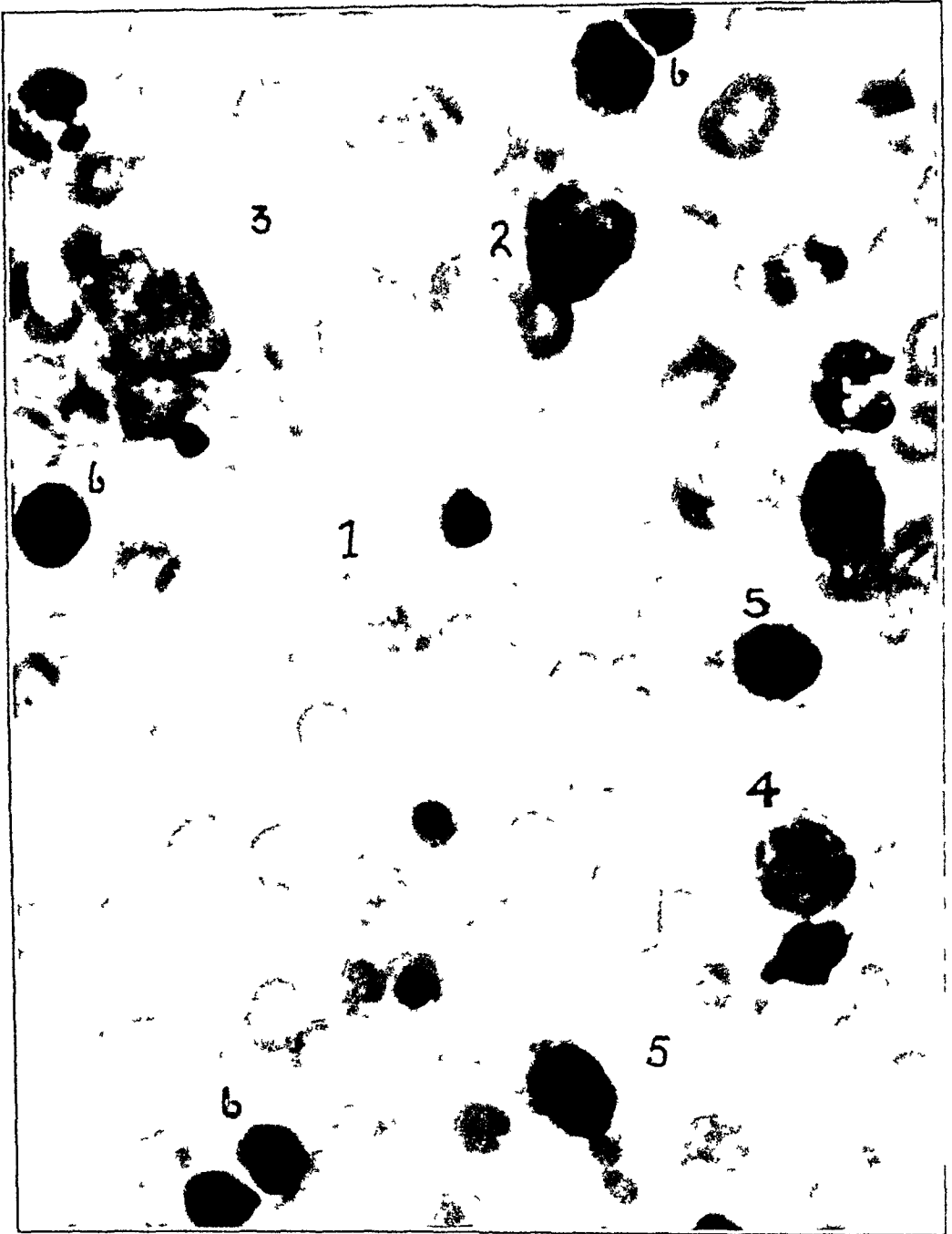


Fig. 4—Blood smear, leukemoid phase, $\times 1,000$, Wright's stain. Numerous atypical platelets are present. One contains a ring formation (1). Five normoblasts are seen. The typical myeloblast contains several nucleoli (2). Another cell has a nucleus of myeloblastic type, containing a single nucleolus, but the cytoplasm displays zones, the outer clear, the inner foamy (3). The promegakaryocyte nucleus has marked chromatin aggregation (4). Two small megakaryocytes have fragmentary granular cytoplasm (5), and numerous naked nuclei of small adult megakaryocyte type are present (6).

these cells, were recognized in the capillaries of the lung. The bronchi showed slight chronic bronchitis.

Liver. Concentrated about the portal triads were many cell-poor, caseating miliary tubercles. Occasional acid-fast bacilli were found. There was some chronic passive congestion. Stains specific for fat showed minimal fatty degeneration.

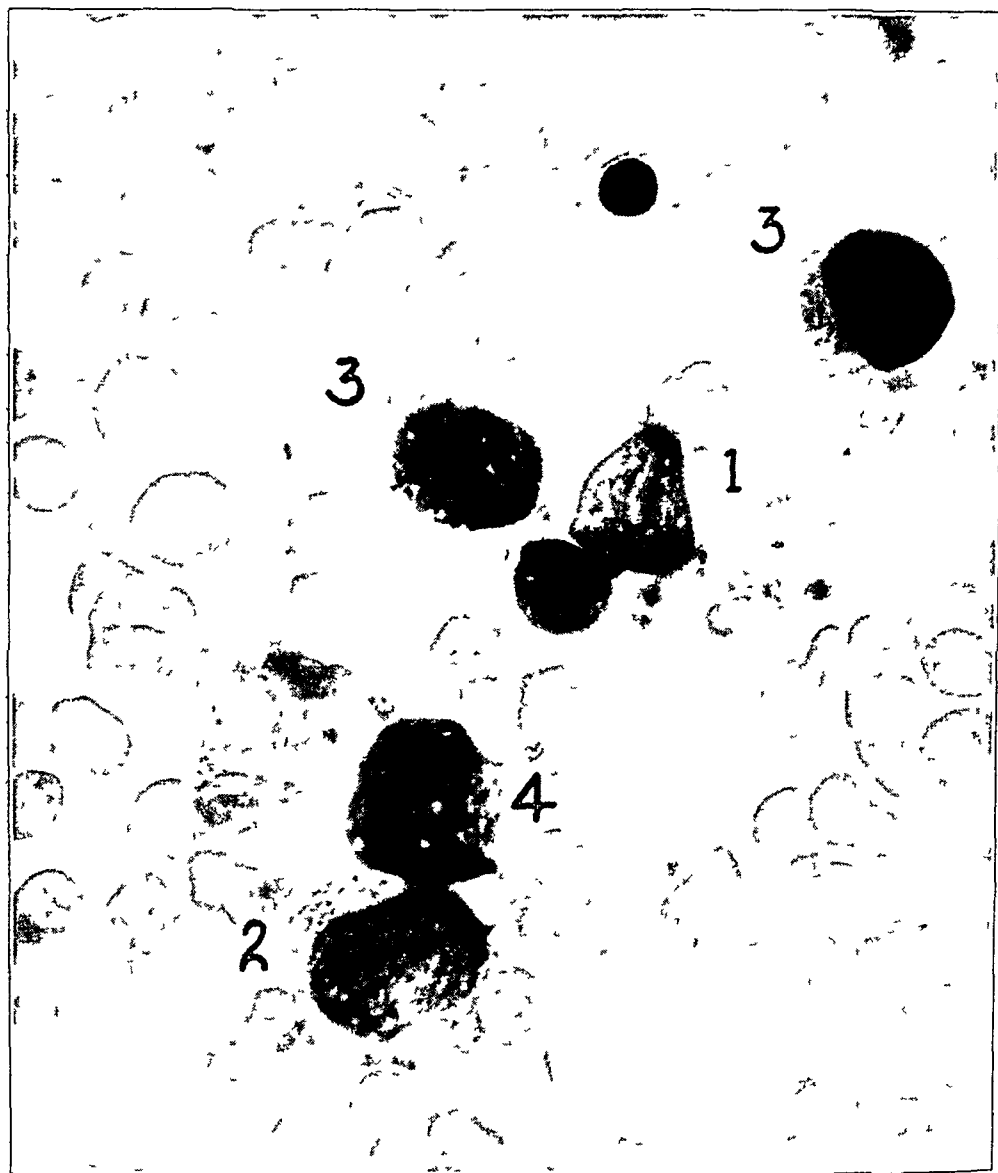


Fig. 5—Blood smear, leukemoid phase, $\times 1,300$, Wright's stain. Present are a myeloblast (1), a myelocyte (2), two small adult megakaryocytes (3) and a naked nucleus of small megakaryocyte type (4).

of the hepatic cells. Specific stains showed moderate amounts of iron in the hepatic cells and in a few Kupffer cells. About many of the portal triads were lymphocytes and a few macrophages. No myelopoiesis was discerned.

Adrenal Glands. In the parenchyma of the right adrenal gland were a few miliary tubercles. The connective tissues in and about the gland were not increased. In the medulla were focal areas of myelopoiesis.

Other Organs The appendix showed fibrosis and slight neurinomatous proliferation. The stomach showed slight infiltration of the submucosa with lymphocytes. The kidneys showed no myeloid tissue, and there were no megakaryocytes, or fragments thereof, in the glomerular tufts. All other organs were normal and showed no myelopoiesis. There were no changes in the single parathyroid removed.

The anatomic diagnosis was as follows: generalized osteosclerosis, generalized myelofibrosis, generalized aplasia of the bone marrow, myeloid metaplasia of the surgically removed spleen and of the adrenal glands, generalized anemia, generalized miliary tuberculosis with massive acute miliary tuberculosis of the lungs and the liver and scattered miliary tubercles in the adrenal glands, the pancreas, the abdominal lymph nodes and the bone marrow, caseonodular tuberculosis of the axillary lymph nodes, chronic appendicitis, bilateral fibrous and fibrinous pleurisy, and a minimal amount of arteriosclerosis.

COMMENT

This case is unique in that in no previous case of this syndrome has there occurred the combination of the leukemoid blood picture with the atypical platelets, together with generalized osteosclerosis and myelofibrosis. In no other case does there seem to have been a terminal leukopenic phase following so high a white cell count.

In our case the blood picture during the phase after splenectomy, when the white cell count was high, was closely similar to that in the case reported by Downey and Nordland (1939), and evolutionary changes similar to those reported by them marked the production of the megakaryocytic series from the myeloblasts. We were also able to observe this derivation in smears from the spleen, but in our sections of the spleen we were not convinced that we could follow this evolutionary sequence. Downey and Nordland, however, in sections of the spleen saw development of megakaryocytes from "basophilic lymphoid hemocytoblasts." It was clear, in our case, that the abnormal platelets were derived solely from the megakaryocyte series, and never from cells established in the granular cell or lymphocyte series. This fact is regarded as justifying the term "atypical platelets" and indicates the identification of these masses as different from that of the multiple irregular protoplasmic masses which may be seen in leukemic myelosis. While leukemoid blood pictures with high white cell counts and many primitive cells have been present in about half the recorded cases, blood pictures of the type here presented have been few. Dubinskaja¹⁴ gave an incomplete description of the alleged megakaryoblasts seen in the case which she reported and mentioned the presence of highly unusual platelet forms. Megakaryocytes "in small numbers" were seen by Hickling in 6 of the 7 cases he reported, but he gave no description of

¹⁴ Dubinskaja, B. Ueber die Riesenzellenformen der Myelose, *Virchows Arch f path Anat* **270** 192, 1928.

their morphologic characteristics Downey, Palmer and Powell¹⁵ also saw atypical platelets along with fragments of megakaryocytes in a case in which, however, they did not perform an autopsy (The case described by Boros,¹⁶ in which there were apparently typical leukemic infiltrations, is regarded as an instance of megakaryoblastic leukemic myelosis)

The extremely low platelet counts recorded were the possible source of multiple hemorrhages in the cases reported by Downey, Palmer and Powell and by Chapman¹⁷ Bleeding, which occurred intermittently for two years in our patient, has been noted frequently (Hueck,¹⁸ Barth,¹⁹ Mozer,²⁰ Assmann,²¹ Stephens and Bredeck,²² Downey, Palmer and Powell, Hickling [6 cases], Emil-Weil and Cleic, Hirschfeld, Mettier and Rusk,²³ and Lindeboom²⁴)

In our case the red cell picture was of the normochromic type, which has been most frequently reported However, the constant presence of macrocytes suggested a possible association with the hyperchromic, macrocytic type recorded by Hugonot and Sohier,²⁵ by Chapman (case 2), by Downey, Palmer and Powell and by Mavros In most cases, as in ours, there has been a constant presence of nucleated red cells²⁶ No abnormality was demonstrated in the fragility of red cells

15 Downey, H, Palmer, M, and Powell, L The Origin of the Megakaryocytes in the Spleen and Liver in a Case of Atypical Myelosis, *Folia haemat* **41** 55, 1930

16 Boros, J V Ueber einen Fall von akuter Megakaryoblasten-leukämie, *Ztschr f klin Med* **118** 697, 1931

17 Chapman, E N Osteosclerotic Anemia, *Am J M Sc* **185** 171, 1925

18 Hueck, G Zwei Falle von Leukämie mit eigentümlichen Blut- resp Knochenmarksbefund, *Virchows Arch f path Anat* **78** 475, 1878

19 Barth, H Ueber Riesenzellbildung bei Leukämie, *Virchows Arch f path Anat* **256** 693, 1925

20 Mozer, J J Les osteoscleroses diffuses et les anémies osteosclerotiques, *Rev med de la Suisse Rom* **47** 802, 1927

21 Assmann, H Beiträge zur osteosklerotischen Anämie, *Beitr z path Anat u z allg Path* **41** 565, 1907

22 Stephens, D J, and Bredeck, J F Aleukemic Myelosis with Osteosclerosis, *Ann Int Med* **6** 1087, 1933

23 Mettier, S R, and Rusk, G Y Fibrosis of the Bone Marrow (Myelofibrosis) Associated with a Leukemoid Blood Picture, *Am J Path* **13** 377, 1937

24 Lindeboom, G A So-Called Aleukemic Megakaryocytic Myelosis, *Nederl tijdschr v geneesk* **82** 3072, 1938

25 Hugonot, G, and Sohier, R Splénomégalie myéloïde megakaryocytaire amyelocythémique et tuberculose, *Sang* **9** 933, 1935

26 Except for the following cases, in which no nucleated red cells were seen (a) Rathery, M F Splénomégalie du type myéloïde sans myelocythémie, *Compt rend Soc de biol* **54** 138, 1902 (b) Donhauser, J L The Spleen as a Hemoplastic Organ as Exemplified in a Case of Splenomegaly with Sclerosis

(determined by Sanford's method). Vaughan and Harrison reported a slight increase in fragility in 2 cases, due possibly to abnormal thickness of the red cells. A temporary initial polycythemic phase was reported by Lehdorff and Zak,²⁷ by Stone and Woodman²⁸ and by Vaughan and Harrison.

Though proof of their different pathogenicities is lacking, osteosclerosis in which the causative agent is a chemical (e g, cyanite) and the juvenile form distinguished by Reiche²⁹ in 1915, usually known as Albers-Schonberg disease, are widely maintained (Schmidt³⁰) to be entities distinct from the nonfragile, less dense osteosclerosis which has accompanied a variety of hematologic syndromes, most commonly in adults, e g, polycythemia vera (Hirsch³¹), aplastic anemia (Schmidt³²) and, far more commonly, various leukemic and leukemoid reactions. Reports of these last have included a few cases of alleged leukemic myelosis, reported earlier (Hueck von Zahn,³³ Schmorl³⁴ Schwarz,³⁵ and Lehdorff and Zak) the recorded histologic observations of which are now difficult to assess. However, the majority of the cases reported earlier and all those more recently reported have clearly been instances of the syndrome with which we are here concerned. The continuing paucity of instances in which osteosclerosis occurs in association with leukemic myelosis (myelogenous leukemia) suggests that this association

of the Bone Marrow, I Exper Med **10** 559, 1908. (c) Hirschfeld (footnotes 3 and 4). (d) Cesa Bianchi, D. Splenomegalia mcloride alucemica, Haematologica **2** 65, 1921. (e) Chapman¹⁷. (f) Mozer²⁰. (g) Zadek, I. Osteosklerotische Anämie, Klin Wchnschr **7** 1848, 1928. (h) Mavros⁷. (i) Anagnostu, J. L. Beitrag zum Studium der systematischen Osteosklerose, Folia haemat **50** 70, 1933. (j) Emil-Weil, Chevalier and See⁹. (k) Tudhope, G. R. Splenomegaly with Myeloid Transformation, J Path & Bact **44** 99, 1937. (l) Hower, T. F. Megakaryocytic Myelosis with Osteosclerosis, *ibid* **45** 383, 1937.

27 Lehdorff, H., and Zak, E. Myeloid Leukämie in Griesenalten mit eigenartigen histologischen Befunden, Folia haemat **4** 636, 1907.

28 Stone, E. M., and Woodman, D. Polycythemia Terminating in Leuco-Erythroblastic Anemia, J Path & Bact **47** 327, 1938.

29 Reiche, F. Osteosklerose und Anämie, München med Wchnschr **62** 944, 1915, Aleukämische Myelose und Osteosklerose, Med Klin **23** 981, 1927.

30 Schmidt, M. B. Osteosklerose, in Henke, F., and Lubarsch, O. Handbuch des speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1937, vol 9, pt 3, p 79.

31 Hirsch, E. F. Generalized Osteosclerosis with Chronic Polycythemia Vera, Arch Path **19** 91 (Jan) 1935.

32 Schmidt, M. B. Ueber osteosklerotische Anämie und Albers-Schonbergsche Krankheit, Beitr z path Anat u z allg Path **77** 158, 1927.

33 von Zahn. Beitrag zur Geschwulstlehre, Deutsche Ztschr f Chir **22** 1, 1885.

34 Schmorl. Leukämie mit Ausgang in Osteosklerose, München med Wchnschr **51** 537, 1904.

35 Schwarz, E. Ein Fall von Leukämie mit Riesenzellenbolie und Osteosklerose, Ztschr f Heilk **22** 294, 1902.

is rare, that osteosclerosis is far commoner in chronic "nonleukemic myelosis," and that one should view the earlier reports of the alleged cases of leukemia with some dubiety

As in the case we report, generalized osteosclerosis in "nonleukemic myelosis" has accompanied a fibrous, aplastic or severely hypoplastic marrow (Chapman, Mozer, Jores,³⁶ Wolf, Anagnostu, Stephens and Bredeck, Mettier and Rusk, Vaughan and Harrison, and Tudhope) Some of these authors saw islands of active myeloid tissue scattered between the fibrous bands Cases such as that reported by Stone and Woodman and that reported by Hewer, in which osteosclerosis was confined to the lower and upper parts of the femur, respectively, indicate that the entire skeleton must be studied In another group of cases the osteosclerotic bone contained a marrow through which a minimal excess of fibrous tissue was scattered but in which the remaining myelopoietic tissue was hyperplastic (Rathery, Askanazy,³⁷ Donhauser, Zadek, and Hagedorn³⁸) Severe pain, which occurred in our case, appears to be a frequent symptom in osteosclerosis (Hueck, Baumgarten,³⁹ Schwarz, Mozer, Zadek, Mavios, Wolf, and Anagnostu)

The bone marrow in cases of "nonleukemic myelosis" without osteosclerosis and (or) myelofibrosis has displayed a wide variety of activities, from hypoplasia (Firket and Campos,⁴⁰ Dubinskaja, and Hickling) to hyperplasia (Levy,⁴¹ Goldschmid and Isaac,⁴² Barth, and Hugonot and Sohiet) Many cases, both with and without osteosclerosis, in which the bone marrow has been hyperplastic have shown proliferation of megakaryocytes out of all proportion to that of other myeloid cells (Michaelis,⁴³ Rathery, Askanazy, Nauwerck and Moritz,⁴⁴ Assmann, Goldschmid and Isaac, Hagedorn, Zadek, Hickling, and Mettier and Rusk)

36 Jores, A Ein Fall von aleukamische Myelose mit Osteosklerose des gesamter Skelettsystems, *Virchows Arch f path Anat* **265** 845, 1927

37 Askanazy, M Ueber extrauterine Bildung von Blutzellen in der Leber, *Verhandl d deutsch path Gesellsch* **7** 58, 1904

38 Hagedorn, K Ueber einen Fall aleukamischer Myelose mit Osteosklerose in einen alten Gicht, *Ztschr f klin Med* **104** 124, 1926

39 Baumgarten, P Myelogene Pseudoleukämie mit Ausgang in allgemeiner Osteosklerose, *Arb a d path Inst zu Tübingen* **2** 499, 1899

40 Firket, J, and Campos, S Generalized Megalocaryocytic Reaction to Saponin Poisoning, *Bull Johns Hopkins Hosp* **33** 271, 1922

41 Levy, M Zur Diagnose der aleukamische Myelose, *Folia haemat* **25** 63, 1919-1920

42 Goldschmid, E, and Isaac, S Endothelhyperplasie als System-erkrankungen des hematopoetischen Apparates, *Deutsches Arch f klin Med* **138** 291, 1921-1922

43 Michaelis, L Ein Fall von riesenzelligen Degeneration der blutbildenen Organe mit eigenartigen Blutbefund, *Berl klin Wchnschr* **38** 496, 1901

44 Nauwerck, C, and Moritz, P Atypische Leukämie mit Osteosklerose, *Deutsches Arch f klin Med* **84** 558, 1905

A number of unique cases bear mention here, though their relation to "nonleukemic myelosis" is not clear. Von Jaksch⁴⁵ (the case of a young adult with alleged leukemia) and Oesterlin⁴⁶ (the case of a child in which the anatomic lesions suggested the syndrome of nonleukemic myelosis) saw cases in which the bony apposition in the osteosclerotic process was principally subperiosteal. Three cases of myelofibrosis in which there was initial polycythemia have been recorded (Stone and Woodman, Vaughan and Harrison, and Lehndorff and Zak). Rosenthal and Bassen⁴⁷ reported 2 cases of polycythemia vera in which osteosclerotic sternal bone was apparent at biopsy, while Hirsch and Markoff⁴⁸ have performed autopsies in cases of long-standing polycythemia vera associated with generalized osteosclerosis. Moreover, a leukoerythroblastic blood picture, with or without anemia, indubitably occurs in polycythemia vera more often than it has been reported (see references cited by Vaughan and Harrison), and, further, an abnormal number of megakaryocytes in the bone marrow, the circulating blood and other tissues has also been observed in this disease (Minot and Buckman⁴⁹ and Friefeld⁵⁰). These considerations have led Vaughan and Harrison to emphasize the possible relationship of myelosclerosis, megakaryocytic leukemia and polycythemia vera. Also not yet to be defined is the relationship of the "nonleukemic myelosis" syndrome with osteosclerosis and (or) myelofibrosis in those few cases in which there is no myeloid metaplasia and which has been considered as "aplastic anemia" (Schmidt, Rhoads and Miller⁵¹). This situation appears to parallel that in cases of other generalized myelopneuses (e.g. carcinomatosis), in which the presence or absence of leukoerythroblastic anemia associated with myeloid metaplasia is controlled by unknown factors.

In chronic "nonleukemic myelosis" the essential myeloid metaplasia is generally confined to the spleen and the liver. A minimal amount of

45 von Jaksch. Demonstration von multiple Periostitis, Berl klin Wchnschr 38 496, 1901, Multiple Periostaffektion mit an myelogene Leukämie mahnender Blutbefund, Ztschr f Heilk 22 8, 1901

46 Oesterlin, E. Ein Fall kombinierter Knochen-Bluterkrankung, Virchows Arch f path Anat 247 589, 1924

47 Rosenthal, N, and Bassen, F. Course of Polycythemia, Arch Int Med 62 903 (Dec) 1938

48 Markoff, N. Die myelogene Osteopathie, Folia haemat 62 337 1929

49 Minot, G R, and Buckman, T E. Erythremia (Polycythemia Rubra Vera), Am J M Sc 166 469, 1923

50 Friefeld, H. Die Rolle der Megakaryocyten bei der Entstehung des polycythaemische Symptomen komplexes, Virchows Arch f path Anat 282 721, 1931

51 Rhoads, C P, and Miller, D K. Histology of the Bone Marrow in Aplastic Anemia, Arch Path 26 648 (Sept) 1938

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48 Markoff, N. Die myelogene Osteopathie, *Folia haemat* **62** 337, 1929

49 Minot, G. R., and Buckman, T. E. Erythremia (Polycythemia) Rubra Vera, *Am J M Sc* **166** 469, 1923

50 Freifeld, H. Die Rolle der Megakaryocyten bei der Entstehung des polycythaemischen Symptomenkomplexes, *Virchows Arch f path Anat* **282** 721, 1931

51 Rhoads, C. P., and Miller, D. K. Histology of the Bone Marrow in Aplastic Anemia, *Arch Path* **26** 648 (Sept) 1938

myeloid tissue has been observed inconstantly in other organs, e g, lymph nodes (Michaelis, Assmann, Hirschfeld, Oesterlin, Barth, and Mettier and Rusk) and kidneys (Levy, Hickling, and Stone and Woodman). In the kidneys, giant cells in the glomerular loops have generally been regarded as embolic in this disease (Schwarz, Assmann, Barth, Wolf, and Speroni and Llamblas⁵²). This relative absence of "infiltrations" has been widely held to be one character differentiating this syndrome from leukemic myelosis, though Hirschfeld (1914) pointed out that limitation of infiltrations is often enough encountered in cases of typical leukemia.

In the liver, myeloid tissue is usually distributed in widely dilated sinuses and is rarely extravascular. In the spleen, it is diffusely spread through the cords of Billroth and within the splenic sinusoids. Not uncommonly the malpighian corpuscles are obliterated by red pulp, hemorrhages and fibrosis are common. Localized islands of myeloid tissue may form small tumor-like masses within the splenic pulp (Barth, Jaffe,⁵³ Favre, Croisat, and Guichard,⁵⁴ Emil-Weil, Isch-Wall, Perles, and Scemama,⁵⁵ and Downey and Nordland). Hirschfeld (1905) saw similar masses in the wall of the small intestine. On account of their rich content of megakaryocytes they have been termed megakaryocytomas (Hewer). The rich distribution of such giant cells in the spleen and elsewhere has arrested the attention of many workers⁵⁶ and has led

52 Speroni, D, and Llamblas, J. Sobre un caso de esplenomegalia con hemacito-eritroblastemia y megacariocitosis tisural, *Prensa med argent* **15** 1513, 1929.

53 Jaffe, R. H. Aleukemic Myelosis, *Arch Path* **3** 56 (Jan) 1927.

54 Favre, M, Croisat, P, and Guichard, A. La myelose aleucemique megacaryocytaire, *Ann de méd* **35** 5, 1934.

55 Emil-Weil, P, Isch-Wall, P, Perles, S, and Scemama. Un cas de splenomegalie myeloïde megakaryocytaire, *Sang* **10** 797, 1936.

56 (a) Michaelis⁴³ (b) Rathery^{26a} (c) Schwarz³⁵ (d) Sternberg, in discussion on Askanazy, M. Ueber extrauterine Bildung von Blutzellen in der Leber, *Verhandl d deutsch path Gesellsch* **7** 58, 1904 (e) Askanazy³⁷ (f) Nauwerck and Moritz⁴⁴ (g) Assmann²¹ (h) Donhauser^{26b} (i) Hirschfeld (footnotes 3 and 4) (j) Cesa Bianchi^{26d} (k) Firket and Campos⁴⁰ (l) Goldschmid and Isaac⁴² (m) Barth¹⁹ (n) Fiessinger, N, and Olivier, H. D. A propos d'un cas d'anemie splenique. Les hemocytoblastoses, *Bull et mem Soc med de Paris* **1** 1193, 1926 (o) Mozer²⁰ (p) Ballin, M, and Morse, P. F. Myelophthisic Splenomegaly, *J A M A* **89** 1671 (Nov 12) 1927 (q) Jaffe⁵³ (r) Dubinskaja¹⁴ (s) Zadek^{26g} (t) Houcke, E. Origine endotheliale des megakaryocytes dans un cas de splenomegalie myeloide aleukemique, *Compt rend Soc de biol* **103** 725, 1930 (u) Downey, Palmer and Powell¹⁵ (v) Wolf⁶ (w) Anagnostu²⁶ⁱ (x) Emil-Weil, Chevalier and See⁹ (y) Emil-Weil, Isch-Wall, Perles and Scemama⁵⁵ (z) Favre, Croisat and Guichard⁵⁴ (a') Hugonot and Sohler²⁵ (b') Hickling⁸ (c') Hewer^{26l} (d') Hirsch³¹ (e') Stone and Woodman²⁸ (f') Lindeboom²⁴ (g') Tudhope^{26k} (h') Downey and Nordland¹³

to the adoption of such names as "megakaryocytic myeloid splenomegaly" (Emil-Weil and associates⁵⁷). Such cells have been held by some earlier authors to be derived from reticulum or reticuloendothelium⁵⁷. They might be confused with the giant cells of a number of other systems, notably the Reed-Steinberg type, the giant cell of the Stengel-Wilson splenomegaly or the syncytial type of giant cell seen in reticuloendothelial reactions, such as that described by Dustin and Weil⁵⁸ and others. In our case there was no doubt that the giant cells were typical megakaryocytes of the type found in bone marrow, and we believe that they derived from myeloblasts.

PATHOGENESIS

The pathogenesis of this syndrome has naturally received considerable attention. It should be stated that no theory has been satisfactorily proved. The earlier viewpoint, that this syndrome represented leukemia (Michaelis, Schwaiz, Schmorl, and Lehdorff and Zak) or atypical leukemia (Hirschfeld, 1905, and Nauwerck and Moritz), was largely succeeded by that of a group of workers impressed by such atypical aspects of this syndrome as the uniform absence of real leukemic infiltrations and the multiplicity of cell types involved in the metaplasia. This group employed such names as pseudoleukemia (Pastore, Wolf) or aleukemic myelosis (Hirschfeld, 1914, Levy, Hagedorn, Arneth,⁵⁹ Jaffé, and others). Di Guglielmo⁶⁰ concluded that the disease was a leukemia of multiple cell types, or "erythroleukemia," a name reminiscent of the "leukanemia" of von Leube⁶¹. It was natural that observation of cases in which extreme osteosclerosis, or myelofibrosis, was displayed should lead to the conclusion that the blood picture and the myeloid metaplasia were compensatory (Askanazy, Donhauser, Oesterlin, Chapman, Mozer, Ballin and Morse, and Zadek). Such a view, however, fails to explain those cases, otherwise exactly similar, in which the bone marrow is hyperplastic. It seems to us that the evidence available postulates the existence of a pathologic stimulus to myeloid metaplasia rather than the existence of a solely compensatory or physiologic stimulus. Thus, Emil-Weil and associates suggested *un syndrome toxico-infectieuse d'étiologies multiples* and appeared impressed by the possible role of tuberculosis (as did Hugonot and Sohler, and Stone and Woodman). The febrile episodes commonly reported in these cases, and

⁵⁷ Downey, Palmer, and Powell¹⁵ Goldschmid and Isaac⁴² Houcke^{56t}

⁵⁸ Dustin, A. P., and Weil, O. La reticulose syncytiale, Sang **10** 1, 1936

⁵⁹ Arneth, J. Ueber die myeloidisch-pseudoleukamische Reaktion (Aleukamische Myelose), Deutsche med Wchnschr **53** 1505, 1927

⁶⁰ di Guglielmo, G. Un caso di eritro-leucemia, Folia med **3** 386, 1917

⁶¹ von Leube. Ueber einen Fall von rapid verlaufender schweren Anämie mit gleichzeitigen leukamischen Beschaffenheit des Blutes, Sitzungsbd phys-med Gesellsch zu Würzburg **3** 46, 1900

present in ours, certainly suggest the possibility of a chronic infection. While our patient may have had tuberculosis localized in the lymph nodes for a number of years, there is no doubt that the extremely destructive, nonreactive tuberculosis was a terminal episode. Similar destructive tuberculosis may terminate leukemic myelosis. The postulate of Vaughan and Harrison is worth examining. Pointing out that all the cell types involved in the abnormal hyperplasia are derived from a common source, the reticulum of Maximow, they expressed the belief that a single common stimulus might affect, in degrees differing from case to case, osteoblasts (osteosclerosis), fibroblasts (myelofibrosis) and the hemopoietic cells (metaplasia, leukemoid blood pictures and polycythemia). Perhaps a similar situation exists in the chronic hyperplasias of lymph nodes (the reticulososes), in which hyperplasia of multipotential cells leads to the development of many different histologic pictures. We feel that at present this affords the most satisfying conception of the syndrome of "nonleukemic myelosis."

SUMMARY

A case of chronic "nonleukemic myelosis" is reported with generalized diffuse osteosclerosis, generalized fibrosis of the bone marrow, an erythromyelomegakaryoblastic blood picture with many atypical platelets and splenomegaly with myeloid metaplasia in which megakaryocytes are frequent. Certain of these features are unique and are discussed in relation to the general characteristics of this syndrome.

We believe that this syndrome may be due to chronic progressive hyperplasia of multipotential mesenchymal tissues caused by an unknown stimulus.

SMALLNESS OR ABSENCE OF INITIAL POSITIVE DEFLECTIONS IN THE PRECORDIAL ELECTROCARDIOGRAM AND CARDIAC INFARCTION

A STUDY OF PATIENTS WHO CAME TO AUTOPSY

FRANK B CUTTS, M D

A HENRY CLAGETT JR, M D

AND

FRANK T FULTON, M D

PROVIDENCE, R I

This study was undertaken primarily to determine the approximate accuracy of the precordial electrocardiogram as taken routinely in a general hospital in making or excluding the diagnosis of anterior cardiac infarction. Chest leads have been used clinically more and more since 1932. Several studies¹ have been made of the variations noted in the precordial electrocardiograms of normal persons, and there have appeared numerous reports² of abnormalities in the chest lead observed in the

From the Heart Station of the Rhode Island Hospital

1 (a) Master, A M. The Precordial Lead in One Hundred and Four Normal Adults, *Am Heart J* **9**:511, 1934. (b) Kossmann, C E, and Johnston, F D. The Precordial Electrocardiogram, *ibid* **10**:925, 1935. (c) Shipley, R A, and Hallaran, W R. The Four-Lead Electrocardiogram in Two Hundred Normal Men and Women, *ibid* **11**:325, 1936. (d) Sorsky, E, and Wood, P. The Use of Chest Leads in Clinical Electrocardiography, *ibid* **13**:183, 1937.

2 (a) Wolferth, C C, and Wood, F C. The Electrocardiographic Diagnosis of Coronary Occlusion by the Use of Chest Leads, *Am J M Sc* **183**:30, 1932. (b) Further Observations upon the Use of Chest Leads in the Electrocardiographic Study of Coronary Occlusion, *M Clin North America* **16**:161, 1932. (c) Wood, F C, Bellet, S, McMillan, T M, and Wolferth, C C. Electrocardiographic Study of Coronary Occlusion, *Arch Int Med* **52**:752 (Nov) 1933. (d) Katz, L N, and Kissin, M. A Study of Lead IV, *Am Heart J* **8**:595, 1933. (e) Wood, F C, and Wolferth, C C. Huge T-Waves in Precordial Leads in Cardiac Infarction, *ibid* **9**:706, 1934. (f) Wolferth, C C, and Wood, F C. Acute Cardiac Infarction Involving Anterior and Posterior Surfaces of Left Ventricle, *Arch Int Med* **56**:77 (July) 1935. (g) Bohning, A, and Katz, L N. The Four-Lead Electrocardiogram in Coronary Sclerosis, *Am J M Sc* **189**:833, 1935. (h) Roth, I R. On the Use of Chest Leads in Clinical Electrocardiography, *Am Heart J* **10**:798, 1935. (i) Faulkner, J M. The Electrocardiographic Diagnosis of Acute Cardiac Infarction with Special Reference to the Value of Precordial Leads, *New England J Med* **213**:1215, 1935. (j) Levine, H D, and Levine, S A. An Electrocardiographic Study of Lead IV with Special Reference to the Findings in Angina Pectoris, *Am J M. Sc* **191**:98,

(Footnote continued on next page)

presence of various types of heart disease, particularly cardiac infarction. In addition, there have been some important investigations³ of direct and indirect chest leads following experimentally induced cardiac infarction in animals.

1936 (k) Edeiken, J, Wolferth, C C, and Wood, F C The Significance of an Upright or Diphasic T-Wave in Lead IV When It Is the Only Definite Abnormality in the Adult Electrocardiogram, *Am Heart J* **12** 666, 1936 (l) Levine, H D The Effect of Various Altered Cardiac Mechanisms on Lead IV, in *Medical Papers Dedicated to Henry Asbury Christian*, Baltimore, Waverly Press, 1936, p 87 (m) Wilson, F N The Electrocardiogram in Diseases of the Coronary Arteries, in Levy, R L Diseases of the Coronary Arteries and Cardiac Pam, New York, The Macmillan Company, 1936, chapt 12 (n) Willcox, A, and Lovibond, J L The Four Lead Electrocardiogram in Coronary Disease, *Lancet* **1** 501, 1937 (o) Master, A M, Dack, S, Kalter, H H, and Jaffe, H L The Significance of an Absent or a Small Initial Positive Deflection in the Precordial Lead, *Am Heart J* **14** 297, 1937 (p) Wilson, F N Recent Progress in Electrocardiography and the Interpretation of Borderline Electrocardiograms, *Proc A Life Ins M Dir America* (1937) **24** 96, 1938 (q) Kossmann, C E, and de la Chapelle, C E The Precordial Electrocardiogram in Myocardial Infarction I Observations on Cases with Infarction Principally of the Anterior Wall of the Left Ventricle and Adjacent Septum, *Am Heart J* **15** 700, 1938, II Observations on Cases of Infarction of the Posterior Wall of the Left Ventricle, *ibid* **18** 344, 1939, III Observations on Cases in Which the Lesions Were Diffuse, *ibid* **18** 352, 1939 (r) Bohning, A, and Katz, L N Four Lead Electrocardiogram in Cases of Recent Coronary Occlusion, *Arch Int Med* **61** 241 (Feb) 1938 (s) Stewart, H J, and Watson, R F The Effect of Digitalis on the Form of the Human Electrocardiogram, with Special Reference to Changes Occurring in the Chest Lead, *Am Heart J* **15** 604, 1938 (t) Edwards, J C, and VanderVeer, J B A Study of the Chest Leads of the Electrocardiogram with an Evaluation of the Positions of the Precordial Electrode, *ibid* **16** 431, 1938 (u) Robinson, R W, Contratto, A W, and Levine, S A The Precordial Lead I Findings for Patients with Normal Hearts and Those with Heart Disease Other Than Myocardial Infarction, *Arch Int Med* **63** 711 (April) 1939, II Findings for Patients with Myocardial Infarction, *ibid* **63** 732 (April) 1939 (v) Vander Veer, J B, and Edwards, J C The Significance of Small and Absent Initial Positive Deflections in the Chest Lead, *Am J M Sc* **197** 663, 1939 (w) Stewart, H J, and Bailey, R L The Effect of Posture on the Form of Precordial Leads of the Electrocardiogram, *Am Heart J* **18** 271, 1939 (x) Master, A M The Electrocardiogram and X-Ray Configuration of the Heart, Philadelphia, Lea & Febiger, 1939

3 (a) Wood, F C, and Wolferth, C C Experimental Coronary Occlusion, *Arch Int Med* **51** 771 (May) 1933 (b) Bellet, S, and Johnston, C G The Effect of Coronary Occlusion upon the Initial Phase of the Ventricular Complex in Precordial Leads, *J Clin Investigation* **13** 725, 1934 (c) Johnston, F D, Hill, I G W, and Wilson, F N The Form of the Electrocardiogram in Experimental Myocardial Infarction, *Am Heart J* **10** 889, 1935 (d) Wilson, F N, Hill, I G W, and Johnston, F D The Form of the Electrocardiogram in Experimental Myocardial Infarction, *ibid* **10** 903, 1935 (e) Wilson, F N, Johnston, F D, and Hill, I G W The Form of the Electrocardiogram in Experimental Myocardial Infarction, *ibid* **10** 1025, 1935

In a review of the literature it became evident that the studies dealing with human material, with a few exceptions, were in large part correlations between the precordial electrocardiogram and the condition of the heart as determined *clinically*. Thus we encountered only 4 reports⁴ which included postmortem study of the heart in 25 or more cases. In several studies the accuracy of the chest lead in diagnosing the presence of cardiac infarction was considerably greater when patients who came to autopsy were considered than when only clinical data were available. Three of the authors, Levine,^{2j} Master^{2o} and Katz,^{2r} who with their co-authors have done considerable work in this field, have indicated the need of further correlation between the precordial electrocardiogram and the observations made on the heart at autopsy. The well known difficulties inherent in accurately diagnosing the presence of cardiac infarction were again noted by Levine and Levine,^{2j} who reported that 4 of 12 patients found to have cardiac infarction at autopsy were not suspected of having this condition while alive. We therefore decided to limit our study to autopsied patients, in an endeavor to reduce the error in our observations as much as possible.

METHODS OF STUDY AND MATERIAL

From January 1934 until Aug. 15, 1937 precordial electrocardiograms were taken in selected cases, chiefly those of patients suspected of coronary occlusion. From the latter date until the present they have been taken routinely with each electrocardiogram. In the earlier years the precordial electrode was the ordinary limb lead electrode, 6 cm by 3.5 cm. Since early in 1938 the smaller circular precordial electrode, 3 cm in diameter, has been used. Except for the period from June 1938 to June 1939, when the precordial electrode was placed in the fourth left interspace at the midclavicular line, it was placed over the point where the apex impulse was observed or was thought to be. Except in a few of the earlier cases the indifferent electrode was placed on the left leg. In January 1938 the lead wires were reversed so that relative positivity of the exploring electrode resulted in an upward deflection in the finished electrocardiogram. Since this time, therefore, the precordial lead used has been lead IV F⁵. However, to avoid confusion, in all subsequent discussion, tables and illustrations in this paper the necessary changes have been made to permit the assumption that all chest leads were taken by the new method.

Sixty-nine patients form the basis for this report and were chosen in the following manner. In the first place, all patients were considered who had had correctly standardized precordial electrocardiograms taken and who had come to autopsy. From this group of several hundred patients only those falling into one of the three following classes were retained: patients whose precordial electrocardiograms showed (1) an absent initial positive deflection or (2) an initial

4 Levine and Levine^{2j} Master, Dack, Kalter and Jaffe^{2o} Bohning and Katz^{2r} Robinson, Contratto and Levine^{2u}

5 Standardization of Precordial Leads. Joint Recommendations of the American Heart Association and the Cardiac Society of Great Britain and Ireland, *Am Heart J* 15: 107, 1938.

positive deflection less than 2 millimeters in amplitude and (3) patients with cardiac infarction of sufficient size to be detected grossly and not included in (1) and (2). A few otherwise satisfactory patients were excluded because the interval between the taking of the electrocardiogram and autopsy was considered too long, and a few additional ones were discarded because postmortem study included no or inadequate study of the heart. There then remained the 69 patients who make up the material for this paper.

Of the 69 patients thus selected, 50 had an interval of seven days or less between the date of the last chest lead and the autopsy. Eight had an interval of one month or more between these two events, but only 1 had an interval of over four months (patient 33). For 31 of the 69 patients two or more precordial electrocardiograms, taken at different times, were available for study. A small negative deflection (Q wave), less than 3 mm in amplitude, before an initial positive deflection (R wave) of normal height was not considered abnormal. If, however, the Q wave exceeded 3 mm in amplitude and was followed by a positive deflection over 2 mm in height, an uncommon occurrence in this group, the initial positive deflection was considered absent (fig 1 D).

Special mention should be made of 3 patients. In none of them did the chest lead show a positive initial deflection and in none of them did the autopsy reveal gross infarction. However, in each instance the autopsy happened to be performed by a relatively inexperienced member of the department of pathology, 2 of the patients had other obvious gross pathologic conditions on which attention was probably focused, and, most important, in each case only one small microscopic section of the heart was preserved for study. Moreover, 2 of the patients, an 86 year old man and a 67 year old hypertensive woman, had clinical histories suggestive of coronary occlusion. The third patient was a 76 year old man with advanced arteriosclerosis and lobar pneumonia. In view of the considerable doubt concerning the postmortem evidence in these 3 patients, we felt that the lesser of two evils was not to include them in the group.

Finally, a few remarks might be made concerning the possible sources of error in this study. Some of the electrocardiograms were taken by the physician in charge of patients with cardiac disease, but most of them were taken by a trained, supervised technician. In view of the consistent results usually obtained in serial tracings, we are confident that the precordial electrode was properly placed in the majority of cases. Secondly, the autopsies, though carefully performed, were routine, and especial attention was not focused on the heart in each instance. Early cardiac infarction and small infarcts can be easily missed, and it is certainly possible that a few were missed in this group of patients. However, we have endeavored to reduce this second source of error to a minimum by careful review of the microscopic sections with the aid of the pathologist in all doubtful cases. On the other hand, when the anatomic diagnosis of cardiac infarction was made, the evidence to support it was incontrovertible.

PATIENTS WITH ABSENCE OF THE INITIAL POSITIVE DEFLECTION
(ABSENCE OF THE R WAVE IN LEAD IV),
PATIENTS 1 TO 30⁶

In this class were included patients 1 to 24, in whom definite infarction of the anterior surface of the left ventricle was demonstrated, patients 25 and 26, who had definite infarction proved microscopically

6 All patients are numbered as they appear in table 1

but not localized grossly, and patients 27 to 30, in whom infarction of the cardiac muscle was not found. Of the patients with infarction, only patient 2 showed a large part of the infarct on the posterior surface of the left ventricle. So far as could be determined from the clinical histories, 13 (50 per cent) of the 26 patients with infarction had a history of acute pain in the chest. None of the 4 patients without infarction had a similar history.

Of these 30 patients with absence of R waves in lead IV we found that 24 (80 per cent) had definite anterior infarction. It would seem reasonable to consider patients 25 and 26 as having definite infarction which was probably anterior in location. The limb leads, so far as they went, suggested anterior localization. Moreover, we have not thus far seen any instance of accurately localized cardiac infarction in a patient with absence of the R wave in lead IV in which the infarct did not involve the anterior surface of the heart. If patients 25 and 26 were admitted as having anterior infarction, the percentage would be raised to 87.

The ST interval in the precordial electrocardiogram was elevated more than 2.0 mm in 16 or 61 per cent of 26 patients with infarction and in none of the 4 patients without infarction. In serial electrocardiograms on the same patient extreme variations in the depth of the initial negative deflection (Q wave in lead IV) were often noted. No significance could be attached to these variations, and they were most likely due to slight changes in the position of the precordial electrode.

The QRS complex in lead IV was conspicuously slurred and of bizarre contour in 2 patients (2 and 16) with infarction (fig 1 H) and in none of the patients without infarction. Of these 30 patients, 2 with infarction (5 and 18) showed in one electrocardiogram a small R wave in lead IV and 1 patient (29) without infarction had in one tracing a normal R wave in lead IV and in another a small one. Thus, as Master and his co-workers²⁰ have noted, a sharp distinction between a small and an absent R wave in lead IV is occasionally impossible. Patient 22 was difficult to classify. As pointed out by Wilson,²¹ among others, an initial Q wave, 3.0 mm or less in amplitude, may occur before the initial positive deflection, or R wave, in precordial leads of normal patients. In patient 22 (fig 1 G) the Q wave in lead IV was sufficiently small to be within normal limits. However, it was grossly slurred and widened. Possibly its amplitude was diminished because of the presence of bundle branch block. At all events, we considered and classified it as an abnormal Q wave in lead IV, suggestive of cardiac infarction. However, as patient 22 was the only one observed with this type of chest lead, further observations will be necessary to establish or disprove the

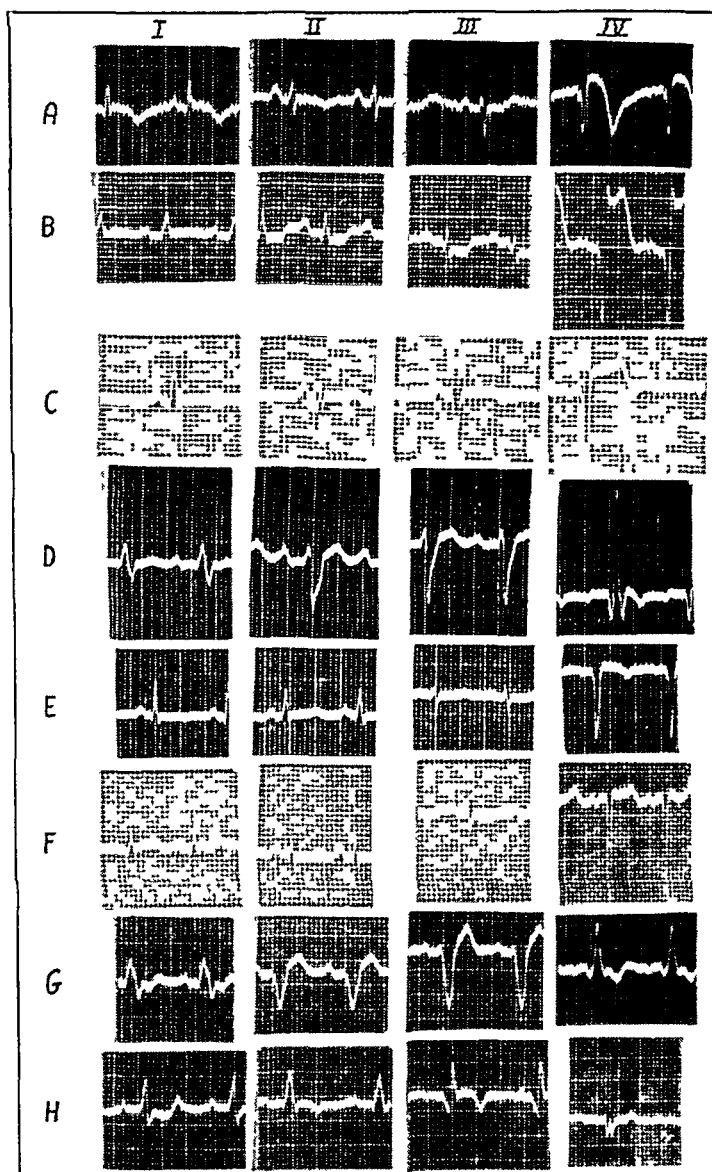


Fig 1—*A*, patient 1 *B*, patient 3 The marked elevation of the ST interval in the chest lead, as contrasted with lead I is evident *C*, patient 4 Here again, the abnormalities in the chest lead are much more striking than those in the limb leads *D*, patient 6 Note the abnormally deep Q wave in the chest lead, practically the only evidence of infarction in this electrocardiogram *E*, patient 8 The absent initial positive deflection in the chest lead is strong evidence for the presence of infarction *F*, patient 11 *G*, patient 22 Note the small but extremely slurred Q wave in the chest lead, discussed further in the text *H*, patient 2 Note the small bizarre deflection in the chest lead As suggested by the limb leads, the larger part of the infarct present was on the posterior surface of the heart These 8 patients were among the 24 with an absent initial positive deflection in the chest lead and with infarction involving the anterior surface of the left ventricle proved at autopsy In this and subsequent illustrations relative positivity of the precordial electrode is represented by an upward deflection in lead IV The numbers of all patients refer to the numbers recorded in table 1

correctness of our impression concerning the significance of this type of Q wave in lead IV. The T wave in lead IV was inverted or diphasic in 19 (73 per cent) of 26 patients with infarction and in 1 of 4 without infarction.

The conventional limb leads were considered positive because of QT or ST interval changes in 12 (46 per cent) of the 26 patients with infarction and in none of the 4 without infarction. However, it should be noted that in only 1 (patient 29, without infarction) of these 30 patients could the limb leads be considered normal (figs 2C and D). Bundle branch block was present in 4 of the 26 patients with infarction (6, 10, 17 and 22) and in 1 (patient 28) of the 4 without infarction. Right axis deviation was not observed.

Of the 4 patients in whom no infarction was found, 3 had only one electrocardiogram taken. Patient 27 (fig 2A) had marked aortic stenosis. Patient 28 (fig 2B), with a history of chronic asthma and hypertension, was distinctly cyanotic and in shock when the electrocardiogram was taken. At autopsy, extreme enlargement of both ventricles, marked coronary sclerosis and thrombosis of the left pulmonary artery were found. Patient 29 (figs 2C and D) was of considerable interest. His first electrocardiogram showed a normal R wave in lead IV. In the course of studying a large mediastinal mass, later found to be an aneurysm, an esophagoscopy examination was made. During this, collapse occurred and a prolonged period of resuscitation was necessary, during which a bronchoscope was kept in the trachea most of one afternoon. After recovery from this episode, roentgen therapy over the chest was instituted. After these two events electrocardiograms showed absence of the R wave in lead IV on three occasions and a small one (0.5 mm) in another tracing. At autopsy a large syphilitic aneurysm of the transverse aortic arch was found. The heart, including the aortic valves and coronary ostia, was normal. In this instance the disappearance of the R wave in lead IV was probably caused by an alteration in the position of the heart, an occurrence which has been observed by Master^{2x}. At the original fluoroscopic examination, before the bronchoscopic examination, the heart was noted to be displaced somewhat to the left, but in study of the series of roentgenograms of the chest, no definite change in the position of the heart could be observed. Patient 30, one with hypertensive disease, had numerous pulmonary abscesses and several hundred cubic centimeters of pus in both pleural cavities. Except for slight enlargement, the heart was normal.

Thus, of these 4 patients with absence of the R wave in lead IV and no infarction, 2 had extreme cardiac enlargement. Master²⁰ and his co-workers and Robinson, Contratto and Levine^{2u} have noted the

occasional absence of the R wave in lead IV when only a considerably enlarged left ventricle was present, and the latter authors observed instances in which the R wave in lead IV was absent in the presence of a large left ventricle except when the precordial electrode was placed exactly at the apex of the heart. Our remaining 2 patients with little or no cardiac enlargement had gross extracardiac, intrathoracic disease which might well have disturbed considerably the position of the heart in the chest. No patient with absence of the initial positive deflection was encountered in whom both the heart and the contents of the thoracic cavity were normal.

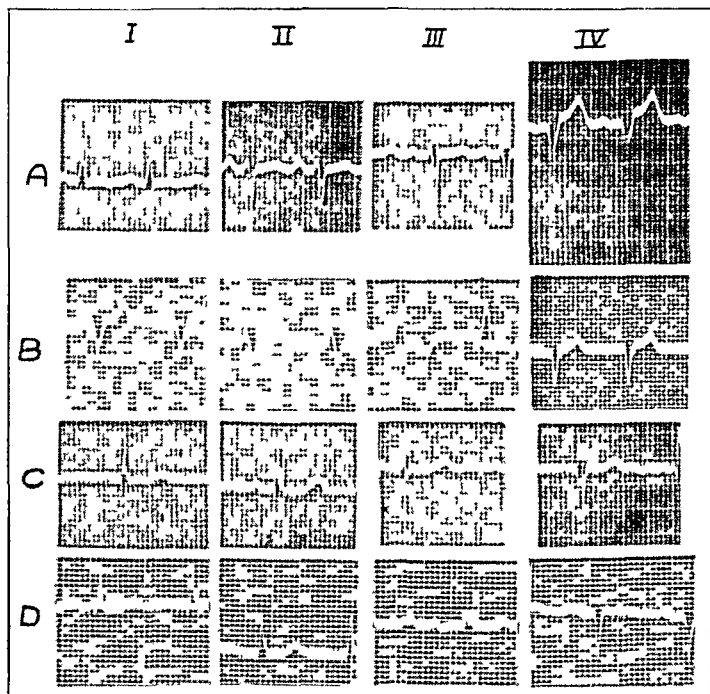


Fig 2—A, patient 27 B, patient 28 C, patient 29 on 1/18/39 D, patient 29 on 3/8/39. Note the disappearance of the initial positive deflection in the chest lead. These 3 patients were among the 4 who had an absent initial positive deflection in the chest lead and had no cardiac infarction at autopsy.

PATIENTS WITH AN ABNORMALLY SMALL INITIAL POSITIVE
DEFLECTION (R WAVE IN LEAD IV),
PATIENTS 31 TO 63

In this class were included patients 31 to 40, with definite infarction of the anterior wall of the left ventricle, patients 41 to 47, in whom the infarction was indefinitely localized or situated elsewhere than on the anterior surface of the left ventricle, and patients 48 to 63, in whom no infarction was discovered. Thus 10 (30 per cent) of these 33 patients had clearcut anterior infarction of the left ventricle. Including patients 41 to 47, 17 (51 per cent) had infarction somewhere in the ventricular muscle. Of the 10 patients with grossly recognizable

anterior infarction, 3 (patients 34, 38 and 40) had infarction of the posterior surface of the left ventricle as well, and in 2 others (patients 35 and 36), the larger portion of the one infarct present was on the posterior surface. From 7 of the 17 patients in whom infarction was somewhere present, a history of an acute attack suggestive of coronary thrombosis was obtained. A similar history was not obtained from any of 16 patients in whom infarction was not found.

In this class of 33 patients, 5 of 14 for whom more than one electrocardiogram was taken had at some time an R wave in lead IV of normal height. Of these 5, patients 34 and 40 had posterior infarction and relatively small anterior infarcts, patient 42 had a small infarct on the anterior surface of the right ventricle, patient 44 had moderate-sized infarction of the interventricular septum and in patient 63 no infarction was present.

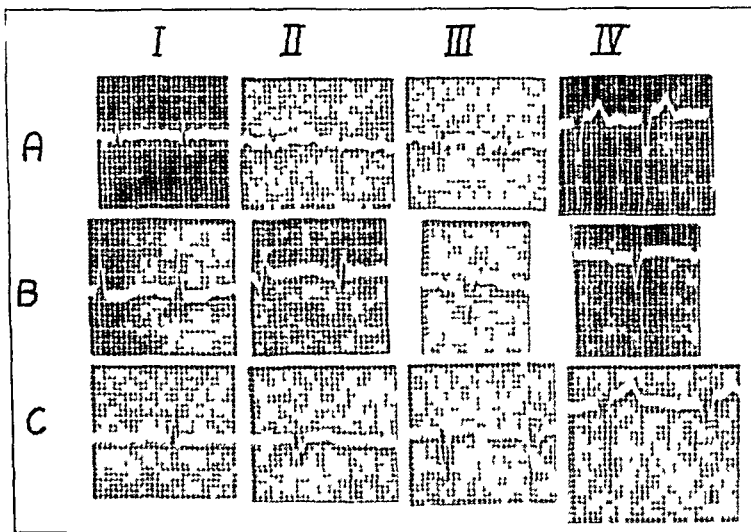


Fig 3—A, patient 32; B, patient 35. In this case, as suggested in the limb leads, the larger part of the infarct involved the posterior surface of the left ventricle. C, patient 40. Note the small Q wave preceding the abnormally small R wave in the chest lead. These 3 patients were among the 10 who had an abnormally small initial positive deflection in the chest lead and definite infarction of the anterior left ventricle at autopsy.

A small downward (negative) deflection, 1 mm or less in depth, was present before the R wave in 3 of the 10 patients with definitely localized anterior infarction (patients 31, 39 and 40, fig 3 C). A similar negative deflection was present in only 1 (patient 50) of 16 patients in whom infarction was not found and was not observed in the 7 patients with definite infarction not clearly shown to involve the anterior portion of the left ventricle. This small negative deflection was observed by Johnston, Hill and Wilson^{3c} to appear occasionally or be accentuated after experimental cardiac infarction and was thought to result from delay in activation of the subendocardial muscle.

Some investigators⁷ expressed the opinion that a small R wave was less significant in diagnosing infarction when the downward deflection following the R wave was small, i e, less than 10 mm in amplitude. In this class, 5 (patients 35, 37, 40, 44 and 45) of 17 in whom infarction was present showed at some time a deflection less than 10 mm in depth following the small R wave. Among the patients without infarction, 3 (patients 48, 50 and 62) of 16 had a downward deflection of less than 10 mm following the R wave. We are therefore rather doubtful of the significance of the size of the deflection following the R wave.

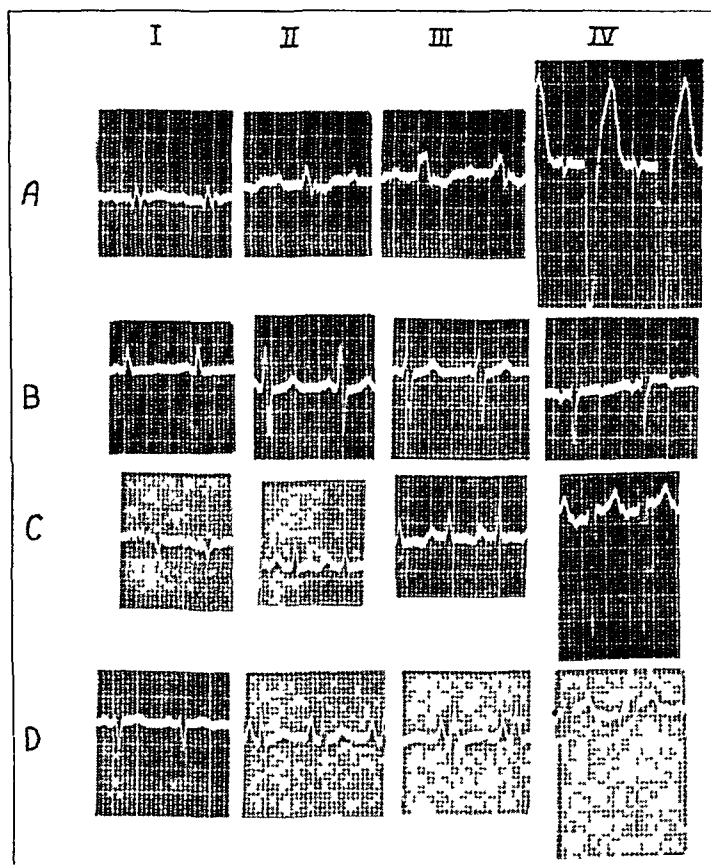


Fig 4—*A*, patient 49. Note the presence of bundle branch block and the considerable elevation of the ST interval in the chest lead. *B*, patient 50. *C*, patient 53. *D*, patient 56. This patient had cor pulmonale. These 4 patients were among the 16 in whom there was an abnormally small initial positive deflection in the chest lead and infarction was not found at autopsy.

In 2 (patients 45 and 47) of the 17 patients with infarction the QRS complex of the chest lead was distinctly abnormal and bizarre in contour. Similar deformity of the QRS complex in lead IV was not observed in any of the 16 patients without infarction.

⁷ Master and others²⁰ Edwards and VanderVeer²¹ VanderVeer and Edwards²²

The ST interval in the chest lead was elevated more than 2 mm in 6 of the 17 patients with infarction and in only 1 (patient 49) of the 16 without infarction (fig 4 *A*). In this patient the limb leads showed definite right bundle branch block. We have recently observed a case of left bundle branch block, in which there was no clinical reason to suspect cardiac infarction or pericarditis, in which the ST segment in lead IV showed similar elevation. Wood et al^{2c} have observed similar elevations of the ST segment in lead IV in the presence of bundle branch block. We do not know the mechanism involved but merely wish to record our belief that, in addition to acute infarction and pericarditis, bundle branch block alone may occasionally be associated with considerable elevation of the ST interval in lead IV.

In 7 of the 17 patients with infarction the T wave in lead IV was diphasic or inverted, while similar changes were evident in 1 of 16

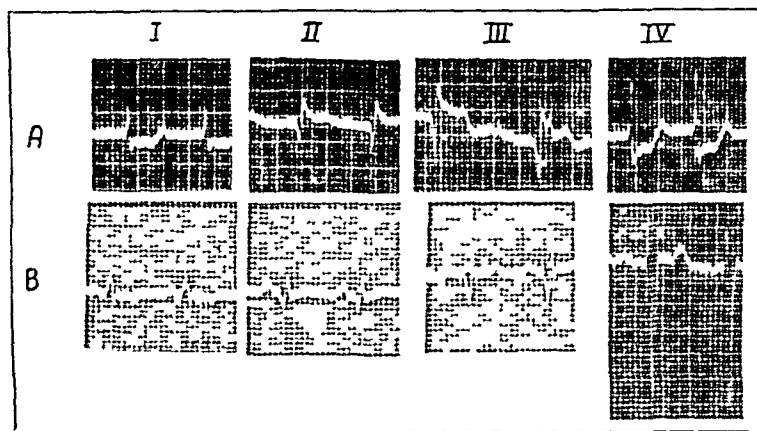


Fig 5—*A*, patient 65. This tracing illustrates the changes in the limb and chest leads in a classic instance of posterior infarction. *B*, patient 68. This patient had, in addition to a posterior infarct, a small anterior infarct whose presence was not indicated in the chest lead. These 2 patients were among the 6 in whom the initial positive deflection in the chest lead was normal and in whom, except for patient 68, infarction was present only on the posterior surface of the left ventricle.

patients without infarction. In general, study of the T wave in the precordial electrocardiogram did not often afford much aid in the diagnosis of cardiac infarction.

Study of the limb leads revealed that in 5 (29 per cent) of the 17 patients with infarction abnormalities were present definitely indicating this diagnosis. Similar definite changes were not present in the limb leads of any of the 16 patients without infarction. Bundle branch block was present in 4 of the patients with infarction and in 5 of the patients without infarction. In none of the patients in whom infarction was revealed was right axis deviation present, while it was present in 2 (patients 53 and 56, fig 4 *C* and *D*) in whom this pathologic finding was absent.

TABLE 1—Data and Precordial Electrocardiograms for the Sixty-Nine Patients Who Came to Autopsy

Num ber, Sex, Age	Date of Electro cardio gram	Fourth Lead					Date of Autopsy, Heart Weight in Gm	Observations Made at Autopsy, Comment
		Q Wave (or Deflection Before R Wave), Depth in Mm	R Wave, Height in Mm	Deflection After R Wave, Depth in Mm	Sr Interval, Elevation or Depression in Mm	Bizarre or W Shaped QRS Complex		
1	10/15/38	7 0 to 9 0			+2 0 to +5 0	No	10/19/38 380	Severe substeral pain, 10/15/38, large in farct entirely through anterior part of left ventricle and interventricular septum near apex
M	10/17/38							
57	10/18/38							
2	11/ 4/35	3 5			0	Yes, W	11/20/35 620	Old fibrous infarct on posterior surface of left ventricle, extending anteriorly just beyond apex, wall thinned
F								
63	8/19/39	13 0			+10 0	No	8/25/39 400	Acute attack 8/18/39, large infarct on anterior surface of left ventricle all through muscle, fibrous pericarditis
3								
70	3/ 9/38	13 0			+4 0	No	3/12/38 400	Acute attack 3/5/38, large infarct on anterior surface, apex ruptured
4								
M								
73	8/25/38	7 0 to 32 0			+3 0 to +4 0	No	9/15/38 610	Acute attack 8/24/38 electrocardiogram, 9/12/38, showed R _s of 2.5 mm, old infarct on anterior surface of right ventricle, recent large infarct on anterior surface of left ventricle
5	8/26/38							
M	8/26/38							
69	9/12/38							
6	7/ 6/38	4 0 to 5 0			0 to +1 0	No	7/15/38 450	Acute pain and dyspnea 6/15/38, large infarct on anterior and lower two thirds of left ventricle, recent infarct (2 cm) on posterior surface of left ventricle
M	7/ 8/38							
66	7/11/38							
7	7/13/38	15 0 to 21 0			+5 0 to +6 0	No	6/11/38 430	Acute pain 6/8/38, large recent infarct on anterior surface of left ventricle
7	6/ 8/38							
M	6/10/38							
61								
8	5/23/38	13 0 to 18 0			+1 0	No	5/26/38 400	Medium sized old infarct at apex of left ventricle
F	5/25/38							
55								
9	3/ 7/38	35 0			+3 5	No	3/11/38 450	Old apical infarct 3.5 cm in diameter
M								
76								
10	4/11/37	3 0 to 12 0			+1 5 to +5 0	No	10/9/37 430	Many anginal attacks, medium sized old infarct involving anterior surface and apex of left ventricle
F	4/17/37							
71	5/ 1/37							
	6/27/37							
	6/ 7/37							
	9/29/37							
	10/ 5/37							

11 M 51	9/27/37	23 0	+1 0	No	↑	Q ₁ T ₁ , low voltage, +	9/27/37 410	Normal R ₄ in 3 electrocardiograms taken on 9/18/37 and before, moderate sized infarct on lower anterior surface of left ventricle, subacute bacterial endocarditis, thrombosis of left anterior descending coronary artery, ? embolism
12 M 71	4/18/37 4/19/37	11 0 to 15 0	+3 0 to +4 0	No	↑ ↓	ST ₁ , ST ₂ elevated, +	4/23/37 470	Acute attack 4/1/37, large infarct on anterior surface of left ventricle and interventricular septum
13 M 62	2/16/34	14 0	+3 0	No	↑ ↓	ST ₁ , ST ₂ elevated, low voltage, +	2/23/34 550	Large infarct all through muscle involving anterior surface of left ventricle and apex
14 M 42	3/13/39 3/14/39	16 0 to 22 0	+1 0 to +5 0	No	↓ & ↑ ↓	Q ₁ T ₁ , low voltage 3/14, ventricular tachycardia, +	3/14/39 700	Acute attack 2/28/39, large infarct on anterior surface of left ventricle through muscle, fibrinous pericarditis
15 M 65	1/ 1/39	25 0	+1 5	No	↑	Small Q ₁ , T ₁ low but upright, ?	2/16/39 810	Old large infarct involving anterior surface and apex of left ventricle
16 M 68	1/10/39 a m, p m	8 0 to 2 0	1 0 to 2 5	No, yes	↑ ↓ & ↓	Auricular flutter, intraventricular block, —	1/10/39 180	Acute attack 1/9/39, large infarct on anterior surface of left ventricle, suspected grossly and proved microscopically
17 M 38	9/ 1/36 9/ 2/38 9/ 3/36 9/ 4/36 9/ 5/36 9/ 8/36 9/15/36 9/19/36 9/26/36	4 0 to 13 0	0 to +1 0	No	↓	Right bundle branch block, —	9/28/36 500	Large infarct of lower anterior portion of left ventricle, extreme involvement of interventricular septum
18 M 69	9/15/38 9/19/38 3/29/39 6/26/39	10 0 to 19 0	+1 0 to +3 0	No	↓ & ↑	T ₁ , T ₂ inverted, +	3/29/39 550	Electrocardiogram on 3/29/39 showed R ₄ just under 1 mm, large old infarct on anterior part of left ventricle near apex
19 M 62		15 0	+6 0	No	↑ ↓	ST ₁ elevated 1 mm, +	6/26/39 520	Bleeding duodenal ulcer, pronounced anemia, recent large infarct of anterior surface of left ventricle and intraventricular septum, doubtful grossly but proved microscopically
20 M 69	9/21/39	14 0	+1 0	No	↑	T ₁ nearly isoelectric, —	9/22/39 550	Angina and pronounced anemia, old anterior infarct at apex with extreme thinning of wall
21 M 65	10/18/37	18 0	+1 5	No	↑	Q ₁ , T ₁ , low voltage, +	10/28/37 510	R ₄ normal 10/16/34, severe attack 10/2/37, large diffuse infarct, fairly recent, on anterior surface of left ventricle
22 M 59	1/28/38 2/ 1/38	1 0 to 1 5	0 to —0 5	No	↓	Left bundle branch block, T ₁ inverted, ?	2/9/39 710	Sudden severe dyspnea 1/26/38, large recent infarct of anterior and lower two thirds of the left ventricle
23 M 72	12/18/39	10 0	+6 0	No	↑ ↓	ST ₁ elevated, ST ₃ depressed, +	1/18/40 410	Severe pain 12/18/39, large infarct on lower one half of interventricular septum and anterior and lateral walls of left ventricle, rupture of left ventricle at apex through area thinned to 2 mm

TABLE 1—Data and Precordial Electrocardiograms for the Sixty-Nine Patients Who Came to Autopsy—Continued

Num ber, Sex, Age	Date of Electro- gram	Fourth Lead				Bizarre or W Shaped QRS Complex	Limb Leads + Diagnostic, —, Not Diagnostic, ?, Questionable	Date of Autopsy, Heart Weight in Gm	Observations Made at Autopsy, Comment
		Q Wave (or Deflection Before R Wave), Depth in Mm	R Wave, Height in Mm	Deflection After R Wave, Depth in Mm	ST Interval, Elevation or Depression in Mm				
24 F 72	1/17/40	12 0			+4 0	No	Q ₁ T ₁ , +	1/17/40 300	Severe pain 1/16/40, recent large infarct on anterior surface of left ventricle extending to apex
25 M 76	10/11/37	1 0			+6 0	No	Low voltage, flat T ₁ , W shaped QRS ₂ , ?	10/11/37 370	Definite acute infarction visible microscopically, not grossly recognized and location indefinite, coronary arteries narrowed no thrombus
26 M 53	3/12/34	18 0			-0 5	No	T ₁ slightly inverted, intraventricular block	4/14/34 430	Severe pain 3/8/34, old extensive infarct of left ventricle seen microscopically but not grossly
27 M 60	8/ 9/38 8/15/38	21 0 to 20 0			+2 0	No	Flat T ₁ , —	9/13/38 380	No pain, extreme aortic stenosis, 1 liter of fluid in each pleural cavity, moderate coronary sclerosis, no infarction
28 F 60	8/ 6/37	7 0			+1 0	No	Nodal rhythm, right bundle branch block, —	8/7/37 6 0	History of hypertension and asthma, extreme cyanosis, 8/6/37, blood pressure 60/? , thrombosis of left pulmonary artery, extreme hypertrophy and dilatation of both ventricles pronounced coronary sclerosis, no infarct
29 M 61	1/18/39 1/28/39 2/ 6/39 3/ 8/39 3/21/39	4 0 to 11 0			0	No	Normal, —	3/21/39 Normal size	1/18/39, R ₁ normal, 3/21, R ₁ 0.5 mm, 1/20 cyanotic and pulseless after esophagoscopic examination, 1/26, roentgen therapy started over chest autopsy large aneurysm of aortic arch, ostiums and lumens of coronary arteries normal, no infarction
30 F 57	3/29/39	16 0			+1 5	No	T ₁ inverted, extreme left axis deviation	3/29/39 390	Moderate hypertension (180/110) bilateral pneumonia with pulmonary abscesses and bilateral emphysema, tuberculosis of mediastinal glands, coronary arteries normal, no infarction, no pericarditis
31 M 40	11/15/38	0 5	1 0	12 0	+1 5	No	Small Q ₁ , flat T ₁ , ?	11/17/38 390	Vomiting, pain and severe dyspnea 11/5/38 subacute large infarct of anterior part of left ventricle
32 M 58	11/ 2/38 11/ 3/38	0	0 5	10 0 to 14 0	0 to +1 0	No	Q ₁ , slight elevation of ST ₁ low voltage, +	11/5/38 425	Angina of two years' duration old medium sized infarct at apex involving left and right ventricles
33 M 44	12/ 7/35	0	1 5	20 0	+1 0	No	Flat T ₁ , T ₂ , —	7/8/36 750	Old areas of fibrosis at apex, about 1 cm in diameter, several small infarcts

31	7/11/38	0	15 to 30	170 to 250	+30	No	↑	Q ₂ , Q ₃ , low voltage, +	7/22/38 170	Angina of fifteen months' duration, old medium sized infarct posteriorly located at base of left ventricle, old infarct (2 cm) anteriorly located at apex
55	7/11/38 7/18/38				+15	No	Flat	Large Q ₂ , Q ₃ , elevated ST ₃ , +	3/26/38 365	Diabetes, abdominal pains 3/18/38, large recent infarct on posterior surface of left ventricle extending down just over apex
35	3/25/38	0	0.5	50		No	↑	Q ₂ , Q ₃ , elevated ST ₃ , +	12/3/37 600	Angina of two years' duration, severe pain 11/12/37, large recent infarct mostly on posterior surface of left ventricle but involving anterior part of apex
70	11/22/37 11/26/37	0	15	110 to 130	0 to +10	No	↑	T ₁ depressed, left bundle branch block, 9/28, auricular fibrillation, ?	10/11/37 450	Diabetes, large subacute infarct involving apex and anterior surface of left ventricle right hemiplegia
50	9/28/37 9/30/37	0	10 to 15	70 to 180	-15 to +15	No	↑ ↓ & ↑	T ₁ depressed, T ₁ flat, ?	3/9/34 600	Severe pain 2/20/34, medium sized old posterior basal infarct, large recent infarct of anterior part of left ventricle and apex
83	2/24/34 2/27/34	0	15 to 0.5	160 to 170	+15 to +25	No	↑	Low voltage flat T waves, W shaped QRS-, ?	3/6/39 630	Severe pains three months previously, large old infarct involving apex and adjacent anterior and posterior surfaces of left ventricle
38	2/21/39 2/1/39	0.5	0.5	270 to 280	+30 to +25	No	↑	T ₁ inverted, intra ventricular block, +	12/1/38 500	Severe chest pain in 1932, on 9/28/38 and 10/21/38, old and recent infarcts involving both anterior and posterior surfaces of left ventricle
40	10/25/38 10/28/38	0.5 to 1.0	15 to 10	190 to 80	+0.5 to +2.0	No	↑ & ↑ ↓	Left bundle branch block, —	12/11/38 310	Normal limb leads and R ₄ , 6/3/37, diffuse infarct recognized microscopically, location uncertain
70	11/3/38 11/9/38 11/28/38	0	0.5	160	0	No	↑	T ₁ slightly inverted, ?	12/22/38 510	Old small infarct of right ventricle, moderate fibrosis but no infarct of left ventricle
41	12/14/38	0	1.0 to 7.0	170 to 250	+15 to +20	No	↑ ↓ & ↑	T ₁ inverted, ?	1/9/39 240	Much fibrosis visible microscopically, definite infarct visible microscopically, but location not clear
59	12/12/38 12/13/38 12/19/38 12/20/38	0	15	130	+15	No	↑ ↓	T ₁ inverted, auricular fibrillation 7/19, left bundle branch block, ?	7/20/39 500	Diabetes, medium sized infarct of lower part of interventricular septum, apparently spreading to adjacent left ventricle, demarcations not stated
13	12/20/38	0	6.0 to 0.5	80 to 90	0	No	↓	Bundle branch block, ? type, ?	6/19/36 490	Death of patient shortly after electrocardiogram, coronary arteries extremely sclerosed, no gross infarct, microscopically numerous confluent areas of necrosis and fibrosis, "spotty" infarction
69	7/3/39 7/11/39 7/19/39	0	10	30	+35	Yes	↑ ↓	Low voltage, —	12/8/36 780	Extreme coronary sclerosis, infarct (2 by 1 cm) of upper interventricular septum, no gross infarct of apex or base of left ventricle, microscopically, moderate fibrosis
15	6/19/36	0	15	110	+10	No	↑			
56	11/20/36	0	15	110	+10	No	↑			
16	11/20/36	0	15	110	+10	No	↑			
56	11/20/36	0	15	110	+10	No	↑			

TABLE 1—Data with Precordial Electrocardiograms for Sixty-Nine Patients Who Came to Autopsy—Continued

Num ber, Sex, Age	Date of Electro- cardio- gram	Fourth Lead					Date of Autopsy, Heart Weight in Gm	Observations Made at Autopsy, Comment
		Q Wave (or Deflection Before R Wave), Depth in Mm	R Wave, Height in Mm	Deflection After R Wave, Depth in Mm	ST Interval, or Elevation or W Shaped Direction of QRS Complex, T Wave in Mm	Bizarre		
47 M 50	10/19/38	?	?	?	+3.0	Yes	10/19/38 405	Acute pain for a few hours, recent thrombus in left anterior descending coronary artery, large infarct seen microscopically, not grossly
48 F 55	10/17/38	0	1.0	7.0	0	No	11/5/38 350	Carcinoma of stomach, no infarct, coronary arteries and pericardium normal, localized areas of hemorrhage and fatty metamorphosis in microscopic sections of myocardium, ? cause
49 M 48	11/25/38 11/26/38	0	1.0 to 0.5	25.0 to 30.0	+10.0 to +9.0	No	11/27/38 460	Cirrhosis of liver, bronchopneumonia moderate coronary sclerosis, no infarction
50 M 63	12/ 8/38	0.5	1.0	9.0	+1.0	No	12/9/38 440	Uremia, blood urea nitrogen 246, no infarction, necrotizing arteriosclerosis
51 M 56	3/27/35	0	1.0	30.0	+1.0	No	4/17/35 580	Syphilitic aortitis with involvement of aortic valve, fibrinous pericarditis, ostiums of coronary arteries extremely narrowed, no infarction
52 M 62	1/11/35	0	0.5	21.0	+1.5	No	4/3/35 580	Aortic stenosis, bilateral empyema coronary arteries normal, no infarction
53 M 25	12/15/38 12/20/38	0	1.0	25.0 to 26.0	+1.5 to +2.0	No	12/26/38 380	Mural thrombi of all heart chambers, infarcts in both lungs, ascites, coronary arteries normal, no infarction, microscopic moderate fatty metamorphosis, ? cause
54 M 65	12/23/36	0	1.0	27.0	+2.0	No	12/24/36 440	Extreme coronary sclerosis, no infarction, moderate diffuse fibrosis
55 M 60	9/23/38	0	1.5	15.0	+2.0	No	9/30/38 460	Bronchopneumonia, extreme coronary sclerosis, no infarct
56 M 42	3/22/38	0	1.5	26.0	+2.0	No	5/9/38 270	Long history of asthma, right ventricle dilated and hypertrophied, coronary arteries normal, no infarction
57 M 55	3/ 2/38 3/ 9/38 3/11/38 3/17/38 3/19/38 3/23/38	0	1.5 to 1.0	19.0 to 31.0	+1.0	No	4/15/38 610	Bronchopneumonia and multiple pulmonary abscesses, antemortem clot at apex of left ventricle, coronary arteries extremely sclerotic, no infarction

58 M	3/28/38	0	15	290	+15	No	↑	Flat T ₁ , intraventricular block, —	3/31/38 470	Extreme aortic stenosis, coronary arteries normal, no infarct
59 M	7/26/37	0	15	280	0	No	↑	Left bundle branch block, —	7/29/37 520	Bronchopneumonia, extreme coronary sclerosis, no infarct
60 M	7/10/37	0	10	120	+05	No	↑	Diphasic T ₁ , —	7/10/37 500	Chronic asthma and bronchitis, moderate enlargement of both ventricles, extreme coronary sclerosis, no gross infarct, numerous focal areas of fibrosis in microscopic sections
61 F	6/28/37	0	10	110	-10	No	↑	Left bundle branch block, —	7/2/37 650	Bronchopneumonia, numerous mural thrombi, pulmonary infarction, extreme coronary sclerosis, no infarct
62 F	3/3/39 3/6/39	0	10	70 to 80	0	No	↑	Low voltage, —	6/19/39 250	Roentgenogram 3/3/39, large amount of fluid in left part of chest, heart pushed to right side, autopsy carcinoma of ovary with generalized metastases, pericardium much thickened by metastases, coronary arteries markedly sclerosed, no infarction
63 M	6/12/39 6/15/39 6/22/39 6/27/39 6/30/39	0	05 to 30	120 to 220	0	No	↑	Intraventricular block, auricular fibrillation, —	7/2/39 600	Moderate involvement of mitral and aortic valves, thrombosis of right pulmonary artery, no infarction of heart
64 M	11/24/33 5/21/38 8/31/38 9/16/38 9/28/38 11/2/38	0	30 to 70	100 to 300	0 to +10	No	↑	Q ₃ , T ₃ , auricular fibrillation, +	11/4/38 110	Old large infarct of posterior surface of left ventricle extending to but not involving apex
65 M	1/19/31	0	120	50	-40	No	↑ ↓	Q ₃ , T ₃ , +	1/20/31 310	Severe pain 1/5/31, recent large infarct of posterior surface of left ventricle with rupture 2 cm above apex
66 F	3/2/38	0	20	350	0	No	↑	T ₁ slightly inverted, ?	3/4/38 310	Acute pain 2/28/38, diabetes, large recent infarct of posterior surface of left ventricle extending to posterior surface of apex
67 M	1/1/38 1/23/38	0	20 to 30	230	+15	No	↑ & ↑ ↓	QRS slightly slurred, —	5/2/38 440	Symphibic aortitis with extreme narrowing of ostium of right coronary artery, old small infarct at posterior base of left ventricle, multiple pulmonary infarcts
68 M	6/15/39 6/22/39 6/24/39	0	110 to 40	150 to 330	0 to +40	No	↑ & ↑ ↓	T ₁ depressed, Q ₂ and Q ₃ , +	7/2/39 520	Healed infarct on posterior surface of right ventricle, recent anterior infarct (15 cm) halfway between apex and base
69 M	7/1/39 7/8/39	0	15 to 30	90	-10	No	↓	T ₁ slightly inverted, ?	8/3/39 650	Old infarct of posterior surface at base of left ventricle, recent infarct on posterior surface near and slightly involving the apex

As regards the 16 patients in whom cardiac infarction was not found, in none could the heart be considered normal. The following pathologic conditions were observed: cardiac hypertrophy, presumably on a hypertensive basis, considerable fatty metamorphosis of the heart muscle, apparent when the muscle was studied microscopically, syphilitic involvement of the aortic valve, aortic stenosis, pericarditis, cor pulmonale (chronic type), rheumatic heart disease, extreme coronary sclerosis, considerable carcinomatous involvement of the pericardium.

PATIENTS WITH CARDIAC INFARCTION OF SUFFICIENT SIZE TO
BE DETECTED GROSSLY, NOT INCLUDED IN THE TWO PRE-
VIOUS CLASSES, PATIENTS 64 TO 69

In these 6 patients with infarction the initial positive deflection was within normal limits. In patient 69 the R wave in lead IV ranged between normal and abnormal limits in the same record, apparently changing with respiration. This variation again illustrated the impossibility of always making a sharp separation between the normal and abnormal precordial electrocardiogram.

All of these 6 patients had posterior infarcts. In addition, patient 67 had syphilitic narrowing of the ostium of the right coronary artery and syphilitic aortitis. Patient 68 (fig 5B) had, in addition, a small anterior infarct and was the only 1 of all 69 patients with both an anterior infarction and a normal R wave in lead IV in all records. However, even in this case there was some suggestive evidence of anterior infarction as the R wave in lead IV became progressively smaller in serial records and the ST interval in lead IV became abnormally elevated. Two of the 6 patients gave a history of acute precordial pain.

Two (patients 65 and 69) of 3 patients with recent posterior infarction had depression of the ST interval in lead IV. In only patient 68 (with anterior infarction) was the ST interval in lead IV abnormally elevated. The T wave in lead IV was diphasic or inverted in 4 of the 6 patients. In 3 of the 6 patients the limb leads gave definite evidence of cardiac infarction.

COMMENT ON THE ENTIRE GROUP, PATIENTS 1 TO 69

In this group of patients there were 54 men and 15 women. Forty-nine patients had cardiac infarction at autopsy, and 20 did not. Of the 34 patients with definite anterior infarction and with absent or small R waves in the chest lead, the larger part of the infarct was on the posterior surface of the left ventricle in 3 (patients 2, 35 and 36). In addition, patient 34 had two separate infarcts, the larger one being on the posterior surface of the heart. In these 4 (patients 2, 34, 35 and 36), the limb leads showed changes in the QT segment char-

acteristic of posterior infarction. Thus in these 4 instances the precordial electrocardiogram, interpreted in conjunction with the limb leads, provided accurate localization of the infarction subsequently found. It could not be predicted whether one extensive or two smaller areas of infarction were present, however.

Among these 34 patients with anterior infarction and with absent or small R waves in the chest lead, there were 3 additional ones (patients 6, 38 and 40) with both anterior and posterior infarction. In these instances the posterior infarct was fairly small or at least smaller than that found anteriorly. In these 3 patients the limb leads gave no definite indication of the posterior infarct. These few cases would suggest that in the presence of both anterior and posterior infarction, the posterior infarct may be indicated in the limb leads, but only if it is of sufficient size relative to the anterior infarct.

Of the total of 49 patients with infarction, 2 with absence of the R waves in lead IV and 2 more with abnormally small R waves in lead IV had slurred, grossly abnormal QRS complexes in lead IV of the type illustrated in figure 1H. None of the 20 patients without infarction had this type of precordial electrocardiogram. Thus, as pointed out by Master and his co-workers²⁰ and Wilson,²¹ this type of QRS complex in lead IV seems highly significant in the diagnosis of cardiac infarction.

Thirty of the 49 patients with infarction and 2 of the 20 patients without infarction had diphasic or inverted T waves in lead IV. Thus the direction of the T wave in lead IV is of some help in diagnosing or excluding the presence of infarction. However, we feel that the direction of the T wave in lead IV, taken by itself, provides little assistance in diagnosis because it may be abnormal in so many other types of cardiac disease. This view is supported by Levine⁸ and his co-workers and by Edeiken, Wolfeith and Wood.²¹

In the 49 patients with infarcts the limb leads provided positive diagnostic evidence in 20 instances, but presented similar evidence in none of the 20 patients without infarction. Thus, *when positive*, the limb leads are of real assistance. From 22 of the 49 patients a definite history of an acute attack strongly suggesting cardiac infarction was obtained, while it so happened that a similar history was not obtained from any of the 20 patients without infarction. Therefore, when present, a typical history of acute persisting substernal pain, perhaps with dyspnea or vomiting, if carefully taken and evaluated, would seem to provide reliable evidence in support of a diagnosis of cardiac infarction.

Bundle branch block was present in 8 of the 49 patients with infarction and in 6 of the 20 without infarction. Thus while the presence

8 Levine and Levine²¹ Robinson, Contratto and Levine²¹

of bundle branch block alone may at times apparently be responsible for a small or even an absent R wave in lead IV, the presence of this conduction defect would seem rather to reduce than to remove entirely the diagnostic significance of smallness or absence of the initial positive deflection in the chest lead. Robinson, Contratto and Levine²¹ have reached similar conclusions.

A study of the ST interval in the precordial electrocardiogram yielded some information of interest. In the 35 patients with clearly localized anterior infarction, the ST interval in lead IV was elevated more than 2.0 mm in 19 (54 per cent). Though the elevation might occasionally occur in the presence of bundle branch block, no patient was observed

TABLE 2—Summary

	Number of Patients	Patients with Definite Anterior Infarction	Patients with Infarction Anywhere in Heart		Number of Patients	History of Acute Chest Pain	Elevation of ST Interval in Lead IV Over 2.0 mm	Depression of ST Interval in Lead IV	Bizarre QRS Complex in Lead IV	Inverted or Biphasic T Wave in Lead IV	Positive Limb Leads	Bundle Branch Block
Patients with absent initial positive deflection in the chest lead	30	24	26	Infarction No infarction	26	13	16	1	2	19	12	4
					4	0	0	0	0	1	0	1
Patients with small initial positive deflection (less than 2.0 mm) in chest lead	33	10	17	Infarction No infarction	17	7	6	1	2	7	5	4
					16	0	1	1	0	1	0	5
Patients with infarction not included above	6	1	6		6	2	1	2	0	4	3	0
All patients	69	35	49	Infarction No infarction	49	22	23	4	4	30	20	8
					20	0	1	1	0	2	0	6

with absence of the R wave in lead IV and an abnormally elevated ST segment in lead IV in whom infarction was absent or in whom it could be demonstrated that the infarct did not involve to some extent the anterior surface of the left ventricle.

Of the entire 49 patients with infarction, 23 showed an elevation greater than 2.0 mm of the ST interval in lead IV and 4 showed detectable depression of the ST interval in that lead. In 2 (patients 6 and 45) of the 23 patients with abnormal ST elevation in lead IV, bundle branch block was present. As regards the 4 patients with depression of the ST interval in lead IV, 2 (patients 65 and 69) had posterior infarction which readily explained this abnormality. In the other 2 (patients 22 and 37) the depression of the ST interval in lead IV was confusing because definite anterior infarction was found at autopsy. However, in both of these patients bundle branch block was present. Moreover, in

the 20 patients without infarction 1 (patient 49) had appreciable elevation of the ST interval in lead IV, and 1 (patient 61) had definite depression of that segment. However, in both of these patients definite bundle branch block was present. Because of these observations we feel that abnormality of the ST interval in lead IV, as well as of the initial positive deflection in the chest lead, must be interpreted with considerable caution in the presence of bundle branch block.

SUMMARY

Sixty-nine patients with precordial electrocardiograms who came to autopsy were studied. These patients were selected from a much larger number because they fell into one of three classes:

- 1 Thirty patients with absence of the initial positive deflection in the chest lead. Eighty-seven per cent of these patients had cardiac infarction, and 80 per cent had definitely localized infarction of the anterior surface of the left ventricle. The limb leads yielded positive evidence for infarction in 46 per cent of the patients in whom this condition was found at autopsy. Of the 4 patients with absence of initial positive deflections and no infarction, 2 had extreme cardiac enlargement and the 2 others with little or no enlargement had gross intrathoracic disease.

- 2 Thirty-three patients with an initial positive deflection of less than 20 mm in the chest lead. Thirty per cent of these patients had definitely localized infarction of the anterior surface of the left ventricle. Fifty-one per cent had infarction somewhere in the ventricular muscle. In the presence of a small R wave in lead IV, a small preceding negative deflection was more common in the presence than in the absence of cardiac infarction. Contrary to some opinions, in our experience the size of the negative deflection following the small initial positive deflection was of no definite significance. In none of the patients without cardiac infarction was the heart normal.

- 3 Six patients with cardiac infarction detectable on gross inspection, not included in the two previous classes. All had normal initial positive deflections, and all had posteriorly located infarcts. One patient had, in addition, a small anteriorly located infarct.

Of the 69 patients, 49 had cardiac infarction at autopsy. In 4 patients with small or absent initial positive deflections and infarction of the anterior surface of the left ventricle, a more extensive area of infarction involved the posterior cardiac wall. In 4 patients with cardiac infarction the QRS complex in the chest lead was grossly abnormal in general contour, while this did not occur in any patient without infarction. The T wave in the chest lead was diphasic or inverted in 30 of 49 patients with infarction and in 2 of 20 patients without infarction. The limb

leads showed diagnostic changes in 20 of the patients with infarction and in none of the others. A typical history of coronary occlusion was recorded for 22 of the 49 patients with infarcts and for none of the patients without infarcts. Bundle branch block was present in 8 of the 49 patients with and in 6 of the 20 patients without infarction. In 54 per cent of the patients with clearly localized anterior infarction, the ST interval in the chest lead was abnormally elevated. In the presence of bundle branch block confusing deviations of the ST interval in the chest lead were occasionally observed.

CONCLUSIONS

- 1 In routinely taken electrocardiograms the absence of the initial positive deflection in chest lead IV F is evidence for the presence of cardiac infarction in the great majority of cases.

- 2 An abnormally small initial positive deflection in chest lead IV F is associated with cardiac infarction in about one half the cases in which it is found.

- 3 A sharp distinction between abnormal and normal initial positive deflections is impossible in a few cases because of variations found in serial records.

- 4 A relatively small, grossly abnormal QRS complex in the precordial electrocardiogram may occur at times and is strong evidence for the presence of cardiac infarction.

- 5 In the presence of extreme cardiac enlargement or gross intrathoracic abnormality some caution is indicated in interpreting a small or absent initial positive deflection. An absent or abnormally small initial positive deflection in lead IV F will rarely occur in the absence of either definite cardiac disease or significant extracardiac abnormality within the chest.

- 6 The presence of bundle branch block renders less reliable any abnormality of the initial positive deflection or of the ST interval in the precordial electrocardiogram.

- 7 In an interpretation of abnormalities in the initial positive deflection of the chest lead, the deviations of the ST interval in lead IV, the clinical history and findings and the evidence provided by the limb leads should all be carefully considered in every case before a diagnosis is attempted.

Assistance was given by the pathologist, Dr B Earle Clarke, and by the assistant pathologist, Dr Robert J Williams.

EPIDEMIC POLIOMYELITIS, RECURRENT ENCEPHALOMENINGORADICULITIS AND FIBROMYOSITIS

IN RELATION TO STREPTOCOCCI OBTAINED FROM A WATER SUPPLY

EDWARD C ROSENOW, M D

ROCHESTER, MINN

The epidemic of poliomyelitis concerned was atypical in many respects¹ Older children and young adults were chiefly stricken Weakness of muscles associated with severe pain and other symptoms indicating involvement of the brain, posterior horns, nerve roots, nerves and muscles was common, whereas complete flaccid paralysis of even small muscle groups was rare Convalescence of patients was often greatly prolonged, but ultimate recovery was usually complete Recurring exacerbations with progression and change of symptoms and lesions occurred in some cases, culminating in a strange and painful disease or state, well designated by the descriptive term "encephalomenin-goradiculitis with fibromyositis" The virus was readily demonstrated in the spinal cord² of patients who died of poliomyelitis during the epidemic but was demonstrated with difficulty in nasopharyngeal washings³ During a study of the epidemic in 1934 it was found that streptococci isolated from the nasopharynx, urine, stools, spinal fluid and spinal cord

From the Division of Experimental Bacteriology, the Mayo Foundation

1 (a) Hart, T M, and Luck, J V Orthopedic Aspect of the Los Angeles County 1934 Poliomyelitis Epidemic, *Am J Pub Health* **24** 1224-1228 (Dec) 1934 (b) Wilson, J C, and Walker, P J Acute Anterior Poliomyelitis Orthopedic Aspects of the California Epidemic of 1934, *Arch Int Med* **57** 477-492 (March) 1936 (c) Rosenow, E C, Heilman, F R, and Pettet, C H Observations on the Epidemic of Polio-Encephalitis in Los Angeles, 1934, *Proc Staff Meet, Mayo Clin* **9** 443-451 (July 18) 1934 (d) Bower, A G, Meals, R W, Bigler, M, Ewing, J, and Hauser, V Clinical Features of Poliomyelitis in Los Angeles, *Am J Pub Health* **24** 1210-1212 (Dec) 1934 (e) Stevens, G M The 1934 Epidemic of Poliomyelitis in Southern California, *ibid* **24** 1213-1214 (Dec) 1934 (f) Meals, R W, Hauser, V F, and Bower, A G Poliomyelitis The Los Angeles Epidemic of 1934, *California & West Med* **43** 123-125 (Aug), 215-222 (Sept) 1935

2 (a) Kessel, J F, Hoyt, A S, and Fisk, R T Use of Serum and the Routine and Experimental Laboratory Findings in the 1934 Poliomyelitis Epidemic, *Am J Pub Health* **24** 1215-1223 (Dec) 1934 (b) Rosenow, Heilman and Pettet^{1c}

3 Paul, J R Trask, J D, and Webster, L T Isolation of Poliomyelitis Virus from the Nasopharynx, *J Exper Med* **62** 245-257 (Aug) 1935 Kessel, Hoyt and Fisk^{2a}

produced symptoms and lesions in animals simulating in important respects those symptoms and lesions characteristic of the outbreak ⁴

In a second study, in 1937, of a series of patients who continued to have symptoms after initial attacks of poliomyelitis, it was found (1) that the virus was not demonstrable, (2) that this strange disease was no longer poliomyelitis but encephalomeningoradiculitis with fibromyositis and (3) that it was caused by a streptococcus related to strains isolated during the epidemic ⁵

The epidemiologic conditions of the original epidemic were as unusual as the clinical manifestations. The incidence of the disease was abnormally high or excessively low in localized areas, sometimes having separate water supplies. It did not spread, as is usual in epidemics of poliomyelitis. There was an abnormally high incidence of multiple instances of the disease, often occurring almost simultaneously in family and other groups living on high hills, in upper stories of apartments and on the high sides of streets along hillsides. The incidence of the disease among physicians and nurses who cared for those ill with poliomyelitis was far greater than has ever been reported in epidemics of poliomyelitis ^{2a}. In all previous and subsequent epidemics of poliomyelitis (nineteen in all) which I have studied, I recall only 2 instances in which nurses or physicians who were exposed contracted the disease. Some unusual factor or factors, it was thought, were operative.

A history of inadequate water pressure, permitting back siphonage under stress, was obtained in nearly all instances which were closely studied, and such inadequate water pressure was repeatedly demonstrated where multiple instances of the disease occurred and where nurses and physicians who contracted the disease lived. These findings and the isolation previously of streptococci from water supplies during epidemics of encephalitis which also remained localized suggested the water supply as a possible source of this infection. A study by special methods of the water supply was therefore made.

The results were reported so far as the facts warranted to the health officers or to those in charge at the time, and measures to correct the defects, if any, were instituted.

The recent demonstrations of the presence of the virus ⁶ in stools of persons having poliomyelitis and in the sewage during epidemic polio-

4 Rosenow, E. C. The Relation of Streptococci to the Viruses of Poliomyelitis and Encephalitis. Preliminary Report, Proc Staff Meet, Mayo Clin **10** 410-414 (June 26) 1935. Rosenow, Heilman and Pettet ^{1c}

5 Rosenow, E. C. Recurring Encephalomeningoradiculitis with Fibromyositis Following Poliomyelitis. A Bacteriologic Study of Sixty-Four Cases, Arch Int Med **64** 1197-1221 (Dec) 1939.

6 (a) Harmon, P. H. The Use of Chemicals as Nasal Sprays in the Prophylaxis of Poliomyelitis in Man, J A M A **109** 1061 (Sept 25) 1937.

myelitis⁷ indicate the importance of the water supply as a possible source of infection. It is the purpose of this report to record the results of my studies made on the relationship of the water supplies to this epidemic and to the instances of encephalomeningoradiculitis and fibromyositis which followed.

CONDITION OF WATER SUPPLY IN RELATION TO THE DISEASE IN PHYSICIANS AND NURSES

On inquiry, it was learned that 48 of about 450 nurses and 9 of 125 interns had contracted poliomyelitis during the month previous to my study. Gastrointestinal symptoms were present in most cases of poliomyelitis and were common among nurses or physicians having mild forms of the disease. Little attention was given to this circumstance because nearly all who contracted the disease had been exposed to patients who had poliomyelitis. The incidence of the disease was far greater among nurses living in cottages near the hospitals than among those who lived on the outside, many of whom had also been exposed to the disease. It was found that most of the nurses lived in a long double row of two story cottages, 12 to 14 nurses in a cottage, thirty-four cottages in all, and that the water supply common to all cottages came from one pipe. The toilet valves were chiefly of the flush type. It was found that a lack of water pressure during rush hours occurred regularly in the cottages at the farther end of the rows, especially on the upper floors. In one cottage at the farthest end, 7 nurses living on the second floor and 1 living on the first floor, or approximately 57 per cent of the 14 nurses living in this cottage, contracted poliomyelitis. Lack of pressure and back suction of air were demonstrated to occur in water outlets in the nurses' rooms and in the bathrooms upstairs when the faucets downstairs were turned on, and the residual water in one of the toilets was seen being drawn back into the drinking system. A linear break in the diaphragm of the flush valve in this toilet was found. In view of the nature of this defect in the diaphragm, it must have existed for some time. Of the 48 nurses who contracted this disease,

(b) Trask, J. D., Vignec, A. J., and Paul, J. R. Poliomyelitis Virus in Human Stools, *ibid.* **111**:6-11 (July 2) 1938. (c) Kramer, S. D., Hoskwith, B., and Grossman, L. H. Detection of the Virus of Poliomyelitis in the Nose and Throat and Gastro-Intestinal Tract of Human Beings and Monkeys, *J. Exper. Med.* **69**:49-67 (Jan.) 1939. (d) Kling, C., Olin, G., Magnusson, J. H., and Gard, S. Nouvelles recherches sur l'élimination du virus poliomyélique par les matières fécales, *Bull. Acad. de méd., Paris* **121**:826-831 (June 13) 1939. (e) Howe, H. A., and Bodian, D. Production of Experimental Poliomyelitis from Untreated Stools, *Proc. Soc. Exper. Biol. & Med.* **41**:538-539 (June) 1939.

7 Paul, J. R., Trask, J. D., and Culotta, C. S. Poliomyelitis Virus in Sewage, *Science* **90**:258-259 (Sept. 15) 1939.

out of the 450 living in the cottages, 26, or 54 per cent, lived in the farthest third of the cottages with respect to the inlet of the water supply, 17, or 35 per cent, lived in the middle third, and 5, or 10 per cent, lived in the nearest third (autogenous contamination)

The conditions were next studied at a second row of cottages which were of similar construction and distribution in relation to the water supply but which were situated on a much lower level, a fact which insured greater water pressure. About 230 orderlies and maids, many of whom also worked in the wards of the contagious disease hospital where patients who had poliomyelitis were cared for, lived in these cottages. Only 2 of these persons had contracted poliomyelitis. The same type of flush toilet valve as was used in the cottages for the nurses was found, but lack of water pressure had not occurred nor could it be demonstrated. The capacity to deliver water under the greatest stress was adequate. The central source of the water supply was the same as that for the nurses' cottages.

- As indicated, 9 of 125 interns had contracted poliomyelitis, whereas the disease had affected only 3 of approximately 3,000 patients and a large personnel in the general hospital. The water supply to the hospital and to the interns' quarters was obtained from an entirely different source than the supply to the cottages of nurses, maids and orderlies and to the hospital for patients with contagious disease. The toilets in the interns' quarters were equipped with flush valves of the same type as those used throughout the hospital. Lack of water pressure and back suction of air under stress at the water outlets were repeatedly demonstrated (autogenous contamination). Because most of the interns, as well as the nurses, who contracted poliomyelitis had worked in the wards with patients who had poliomyelitis, no one suspected the water supply. One physician who was in charge of the care of patients suffering from poliomyelitis and who lived and was cared for in a small apartment in the contagious disease hospital had a severe and painful attack which continued with recurring exacerbations for many weeks. Lack of water pressure with back suction under stress was repeatedly demonstrated in his apartment (autogenous contamination). The hospital and sanatorium where most of the patients who had encephalomeningoradiculitis and fibromyositis were cared for in 1937 were also equipped with the flush type of toilet valve. Lack of pressure on the upper floors and back suction of air under stress were repeatedly demonstrated (autogenous contamination). Exacerbations of symptoms among this group of patients and a frequent, often almost simultaneous, occurrence among the nurses in attendance of symptoms which were milder but still true to type suggested a common cause, such as a contaminated water supply.

METHODS OF STUDY

Through the cooperation of the health and water departments many specimens of water representing the more central sources routinely examined by them became available for culture. In addition, I made cultures of many samples obtained at the very periphery of the water supplies at which multiple instances of the disease occurred and made control cultures of samples obtained at points at which no instances of the disease occurred during the epidemic of 1934 and in connection with the instances of encephalomeningoradiculitis and fibromyositis in 1937. (By "periphery" and "peripheral water supplies" is meant the drinking water obtained from faucets for occupants in rooms, apartments, houses, cottages and hospitals, in contradistinction to water collected from large water mains nearer the source of the central supply.) The samples of water that were cultured were collected and handled with the usual precautions for insuring sterility. It was taken for granted and very early found true that the usual precautions employed to safeguard the water supply, as determined by standard methods, had been taken. In fact, this safeguarding was elaborately and efficiently done. The standard methods, as well as my method of examination, disclosed that the bacterial count, as determined by formation of colonies, was uniformly low and that *Escherichia coli* was nearly always absent. The method I used in culturing water was similar to the one used successfully for the isolation of causative streptococci from the nasopharynx, spinal fluid, blood, brain, spinal cord and excised muscles and ovaries of patients.

Three cubic centimeters of the water was added routinely to a tall tube containing approximately 17 cc of dextrose-brain broth, and 30 to 45 cc amounts of the sample were added to tall bottles containing 200 cc of dextrose-brain broth. The dextrose-brain broth was usually freshly prepared. To the remaining amount of the sample of water the contents of two tubes of dextrose-brain broth were added, the openings of tubes and bottles were flamed meanwhile. Similar cultures of sterile water were often made to control the technical procedures, and the results were always negative. Parallel cultures made in the beginning on blood agar never yielded the streptococci, whereas those in plain or dextrose broth yielded the streptococci only occasionally. Hence, only mediums containing brain tissue were used routinely. All inoculated mediums were incubated at 33 to 35 C. Various methods were used to separate the streptococci from other bacteria in mixed cultures, for identification and experiments on animals. Plating on blood agar did not usually suffice, if it did, the streptococci obtained usually either had lost their virulence or represented nonvirulent strains. Heating the water itself at 50 C or heating the mixed culture of bacilli and streptococci in dextrose-brain broth for one hour at this temperature often sufficed. But by far the best method consisted of making serial dilution cultures in dextrose-brain broth or soft dextrose-brain agar.⁸

RESULTS OF CULTURES

The streptococci in the primary culture of water were often extremely pleomorphic. Gram-positive or gram-negative diplostreptococci, which often were elongated and sometimes resembled bacilli (fig 1 *a*), were by far the most common forms obtained in the primary cultures. These

⁸ Rosenow, E. C. Isolation of Bacteria from Virus and Phage by Serial Dilution Method, Arch Path 26 70-76 (July) 1938

were nearly always gram-positive when gram-positive bacilli (*Bacillus subtilis*) also grew and were gram-negative when mixed with gram-negative bacilli, usually of the *Pseudomonas* group. After several cultures in dextrose-brain broth (fig 1*b*) or after animal passage (fig 1*c*) the morphologic appearance became uniform and typical. Streptococci were almost never obtained from samples containing *Esch coli*.

All of 15 samples of water collected for several weeks from the cottage in which 8 of 14 nurses contracted poliomyelitis yielded the streptococci, and the first few also yielded *Esch coli* after back siphonage was demonstrated, whereas only 1 of 7 samples obtained from the water at the inlet to the row of nurses' cottages yielded the streptococci and

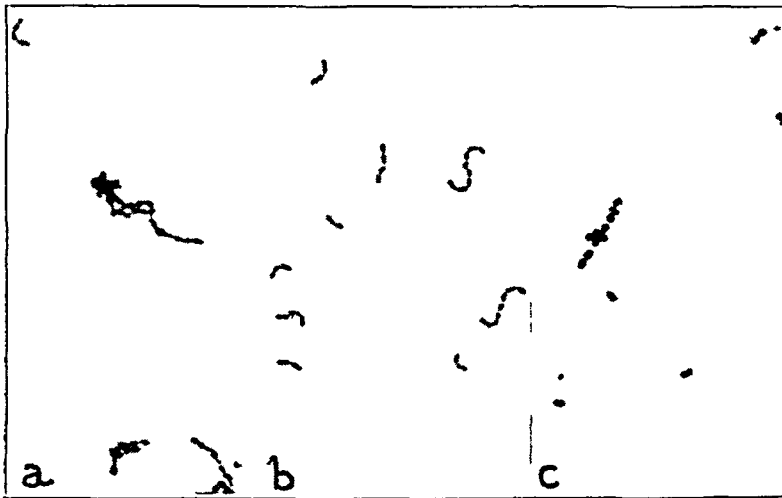


Fig 1—Streptococci isolated from the water supply of patients who had encephalomeningoradiculitis and fibromyositis in 1937 (a) on isolation, (b) in dextrose-brain broth from the end point of growth in the serial dilution culture and (c) after animal passage. Gram's stain, $\times 1,000$.

none yielded *Esch coli*. Cultures of samples collected at the periphery and inlet to the row of cottages where only 2 cases of poliomyelitis occurred did not yield streptococci. Streptococci were obtained from cultures of the water from faucets in the interns' quarters used for drinking purposes by those who became ill far more often than from similar cultures of specimens obtained from the water supply for patients in the general hospital. Specimens of the water supply from the apartment of the physician-patient who lived in the contagious disease hospital repeatedly yielded the streptococci. The streptococci were not obtained from samples of water collected in the wards and kitchens throughout the contagious disease hospital. Repeated cultures of the water at the inlets to the hospital and sanatorium wherein the patients who had encephalo-

meningoradiculitis were cared for yielded streptococci much less often than did those of the water obtained from faucets supplying the drinking water for the patients

Streptococci were isolated much more frequently from samples of supplies to the epidemic region than from samples of supplies to regions in which few or no instances of the disease occurred (table 1). The incidence of isolation of the streptococci from the samples obtained from central water supplies at the time of the epidemic as well as four months later was higher than the incidence of isolation from similar supplies outside the epidemic zone at the time of the epidemic. In one experiment 39, or 65 per cent, of 60 specimens of water from the region wherein poliomyelitis was prevalent yielded the streptococci, whereas only 1, or

TABLE 1—*Incidence of Isolation of Streptococci from Water Supplies with Relation to an Epidemic of Poliomyelitis and to Cases of Encephalomeningoradiculitis and Fibromyositis*

Source of Samples	Relation of Epidemic or Cases	Specimens	Growth of Streptococci in Dextrose Brain Broth	
			Number	Per Cent
Water mains of different supplies	Area of epidemic	95	32	34
	Four months after epidemic	40	11	28
	Outside area of epidemic at time of epidemic	37	4	11
1934	Within area of epidemic	80	39	65
	Outside area of epidemic	43	6	14
	Cottages and quarters where many instances occurred	26	23	88
Periphery	Cottages and quarters where few instances occurred	23	6	26
	Family groups in which 2 or more instances occurred	19	18	94
	Hospital where patients who had encephalomeningoradiculitis and fibromyositis were cared for	15	13	87
Total periphery where many instances occurred		120	93	77
Total periphery where few or no instances occurred		66	12	18

about 4 per cent, of 27 specimens obtained from uninfected regions yielded streptococci. In another experiment the advantages of the dextrose-brain broth method over the standard methods were also strikingly shown. Thus, 17, or 35 per cent, of 48 specimens, revealed diplococci or streptococci in dextrose-brain broth, in contrast to 4, or 8 per cent, of the same 48 specimens cultured in the litmus-lactose broth. In general (table 1), the incidence of isolation was highest from samples obtained from the periphery within the epidemic zones wherein but 1 instance of the disease occurred in family groups (65 per cent), at cottages and quarters wherein many persons contracted the disease (88 per cent) in family groups wherein 2 or more persons contracted the disease (94 per cent) and at the hospital wherein the patients who had encephalomeningoradiculitis and fibromyositis were cared for (87 per cent), an average of 83.5 per cent. This was in sharp contrast to the incidence of isolation from samples of water from the periphery

outside the epidemic area (14 per cent) The incidence of isolation of the streptococci was far lower from samples of water obtained from chlorinated supplies than from samples from unchlorinated supplies Thus, of 17 samples (of 48 cultured) yielding streptococci, the water was unchlorinated in 14 and was chlorinated in only 3

In order to determine the number of viable streptococci in the water, serial dilution cultures in dextrose-brain broth and dextrose-brain agar and dextrose broth in multiples of ten were made The growths obtained often indicated the presence of exceedingly large numbers of streptococci One sample, after being transported to Rochester, Minn., in a sealed bottle, yielded streptococci in dextrose-brain broth in dilutions up to 1 10,000,000,000, in dextrose-brain agar up to 1 100,000,000 and in dextrose broth up to 1 10,000 To be certain of this seemingly impossible result, dilution cultures in dextrose-brain agar were repeated at the same time by four persons in different rooms, with essentially the same result Dextrose-brain broth exposed to the air in open Petri dishes and in open tubes as a control during the period of making cultures remained sterile in every instance

ANIMAL EXPERIMENTS

Mice, rabbits and monkeys were fed the contaminated water and were given injections of water and of streptococci obtained from the water Both pure and mixed cultures were administered before and after animal passage As controls, similar injections of sterile dextrose-brain broth or other mediums used in cultivating the streptococci, of distilled water, of boiled or autoclaved water and of water to which tincture of iodine had been added in a concentration of from 1 30,000 to 1 1,000,000 were made, always with negative results The methods of injection and the amounts administered were comparable with those employed in experiments with streptococci obtained from patients⁹ Routinely, 1 cc of the raw or sterile water was given intracerebrally to rabbits 3 to 5 cc was given intracerebrally and 5 to 10 cc was given intravenously to monkeys and 2.5 to 3.5 cc was given intraperitoneally to mice To rabbits was administered 0.1 cc intracerebrally, and to monkeys 0.5 cc, of 1 1,000 dilutions of dextrose-brain broth cultures containing the streptococci Some monkeys, in addition, received 5 to 10 cc of the undiluted culture intravenously

Results of Direct Injection of Contaminated Water into Animals—The streptococci in the contaminated water both during the epidemic and in 1937 were virulent for mice Thus, the injection of a total of 68 samples intraperitoneally into 147 mice was followed by the death of 103, or 70 per cent, of the mice Cultures in dextrose-brain broth were

⁹ Rosenow, Heilman and Pettet^{1c} Rosenow⁵

made of the peritoneal fluid, blood, muscles or ovaries of 72 mice, streptococci were isolated in 50 mice, or approximately 70 per cent. Thirty-seven samples shown to contain the streptococci were injected into 36 rabbits and 16 monkeys during the epidemic. Paralysis developed in 11, or 30 per cent, of the rabbits and in 6, or 37 per cent, of the monkeys, and the streptococci were isolated from pipetings from the brains of all the animals that died.

Results of Injection of Cultures of the Streptococci into Animals—The results of injection of freshly isolated strains of streptococci obtained from the water representing the supply of patients who had poliomyelitis during the epidemic and of the patients who had encephalomeningoradiculitis were highly specific (table 2). The incidence of paralysis and of lesions of the brain and of the medulla after injection of the streptococci obtained from the water during the epidemic was much

TABLE 2—*Incidence of Characteristic Symptoms and Lesions in Rabbits and Monkeys After Inoculation of the Streptococci Isolated from Water*

Water Supplies	Strains of Strep- tococci	Animals	Symptoms (Per Cent)			Lesions (Per Cent)			
			Pain	Paral- ysis	Spasms	Brain or Medulla	Dura	Nerve Roots	Muscles
During epidemic of polio- myelitis, 1934	35	190	12	47	9	32	25	13	17
After epidemic of polio- myelitis, 1934	9	48	0	3	0	11	0	0	0
Instances of recurring en- cephalomeningoradiculitis with fibromyositis, 1937	34	73	62	23	36	15	45	55	92

higher than that after injection of the water four months after the epidemic had disappeared and after injection of the water from the supply of the patients who had encephalomeningoradiculitis. The incidence of evidence of pain, spasms and lesions of the dura, nerve roots and muscles, the very tissue especially involved in patients, was far greater among those animals which received injections of streptococci obtained from the water supply of the patients who had encephalomeningoradiculitis than it was among those receiving the streptococci obtained from the water supply during and after the epidemic.

Streptococci were isolated in dextrose-brain broth cultures of the brain, spinal cord, muscles, ovaries or blood of nearly all the animals that died. Congestion of the brain and edema and hemorrhagic infiltration of the cauda and the overlying dura, the roots of the lumbar nerves and the lumbar or intercostal muscles were found in nearly all of the animals. The results obtained with these animals were almost identical with those obtained with animals that received the streptococci isolated from patients.⁹

Results of Feeding Animals the Water from Which the Streptococci Were Isolated—Feeding the water from which the streptococci were isolated, that is, water from the same supply as that used by patients who had poliomyelitis, to rabbits for two weeks during the epidemic sufficed to cause paralysis with death in 14, or 39 per cent, of 36 young rabbits in three to seven days. No apparent ill effects were noted in the animals that survived for eight days. Cultures, in dextrose-brain broth, of the pipetings of the brain, spinal cord and cerebrospinal fluid of those that



Fig 2—(a) lymphocytic and leukocytic infiltration in and surrounding lumbar nerve roots, (b) perivascular lymphocytic infiltration at the base of the brain of monkeys following intracerebral and intravenous injection, during the epidemic of 1934, of a pooled sample of water containing the streptococci, and (c) perivascular lymphocytic infiltration at the base of the brain of monkeys following inoculation of the brain emulsion containing the streptococci in the fifth animal passage. Hematoxylin and eosin, $\times 100$

died yielded the streptococci. A mixture of 2 specimens of water obtained from the water supply of patients who had encephalomeningo-radculitis with fibromyositis, and from which water the streptococci had been isolated, was fed untreated to 12 rabbits and 24 mice, and after treatment with tincture of iodine (1:30,000) to 12 rabbits and

24 mice The tincture of iodine killed the streptococci almost instantaneously The untreated and the sterilized specimens of the water were supplied in the drinking cups or in bottles for seven days, at the end of which time the animals were killed with ether and cultures were made immediately by placing peritoneal fluid and pieces of tissue about 0.25 cc in volume in dextrose-brain broth The streptococci were isolated from the muscles of 17, from the liver of 17, from the spleen of 24, from the peritoneal fluid of 7, from the kidney of 9 and from the ovaries of 15 of the 36 animals that received the untreated specimen of water In contrast, the streptococci were isolated from the spleen of only 3 mice, from



Fig 3—Edema and leukocytic and lymphocytic infiltration (a) of the dura over the lumbar region and (b) in and surrounding the lumbar nerve roots following intracerebral and intravenous injection of the streptococci referred to in figure 1 a Hematoxylin and eosin, $\times 105$

the liver of only 1 rabbit and from the muscles, liver, peritoneal fluid, kidney or ovaries of none of the 36 animals that received the sterilized water None of the animals of either group became paralyzed The high incidence of isolation of the streptococci from muscles, kidney and ovaries is in keeping with the clinical findings in the group of patients with encephalomeningoradiculitis with fibromyositis

Microscopic Lesions in Injected Animals—Sections revealed distinct, localized lymphocytic and leukocytic, often perivascular, infiltration of the meninges, especially of the dura in the lumbar and caudal region,

of the lumbar nerve roots and sheaths (fig 2 *a*) and of the choroid plexus in animals that died in from one to five days. Lymphocytic infiltration was chiefly found in these regions in animals that died or that were anesthetized in from six to ten days after injection. Sections of the brain (fig 2 *b* and *c*) revealed perivascular infiltration and other lesions typical of encephalitis. Degeneration of ganglion cells in the spinal cord and hemorrhage and edema in the anterior and posterior horns were common.



Fig 4—Hemorrhagic edema and infiltration of fascia and muscles of the dorsum of (*a*) the forearm of a monkey and (*b*) the foreleg of a rabbit following intravenous injection of the streptococci (*a*) as isolated from the water and (*b*) after preservation in dextrose-brain broth without transfer for one and a half years.

Striking as are the statistical figures given in table 2, they do not give an adequate idea of the markedly specific effects of the streptococci as seen at necropsy. The lesions, especially those of the dura (fig 3 *a*), nerve roots (fig 3 *b*), muscles and fascia (figs 4 *a* and *b* and 5 *a* and *b*), of the ovaries and less often of the stomach, kidney, ureter and bladder, were most striking. The streptococci, usually occurring as diplococci, were demonstrated in the lesions of the dura (fig 6 *a*), nerve roots (fig 6 *b*) and fascia and muscles (fig 6 *c* and *d*).

The streptococci in some samples of water lived for many months when stored in sealed vials in the dark at room temperature. The streptococci isolated from time to time in dextrose-brain broth and in



Fig 5—Interstitial edema with degeneration and cellular infiltration of muscle fibers following intravenous injection of the streptococci (a) into a monkey and (b) into a rabbit. Hematoxylin and eosin, $\times 110$ and $\times 90$.

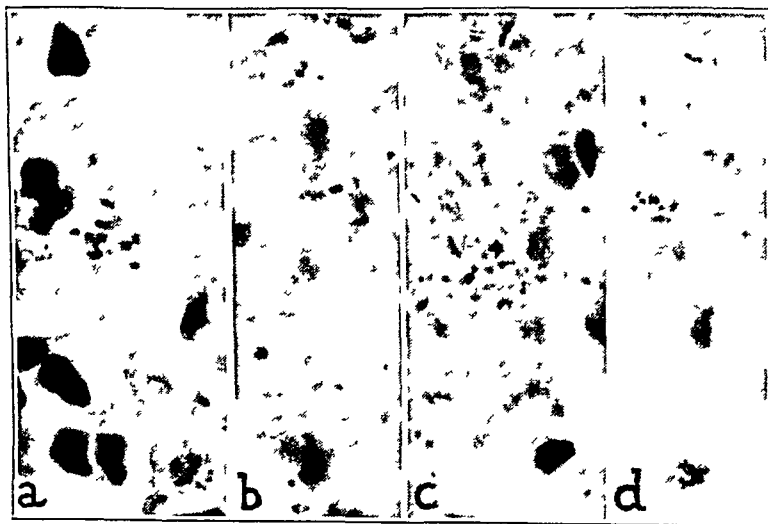


Fig 6—Diplococci in the lesions (a) of the dura shown in figure 3 a, (b) in the sheath of nerve roots shown in figure 3 b, (c) in fascia and muscles shown in figure 5 a and (d) in muscles shown in figure 5 b. Modified Gram's stain, $\times 1,000$.

dextrose-brain agar during the period of storage repeatedly caused lesions in animals, chiefly lesions of the dura, nerve roots, fascia and

muscles (fig 4 b), but changes in virulence, localization and cataphoretic velocity occurred in accord with current epidemics of infections of the respiratory tract and other parts of the body

The evidence of causal relationship between the streptococci obtained from the water and the diseases in question was not limited to morphologic or cultural characteristics or to virulence. The streptococci obtained from both water and patients had respective characteristic distribution curves of cataphoretic velocity^{6b}. Agglutination experiments performed by the special methods previously used^{6b} with pooled suspensions of the streptococci isolated in 1934 and 1937 from the respective water supplies and the serums of patients and of well persons both with and without contact with the disease yielded evidence of specificity and causal relationship.

SUMMARY AND CONCLUSIONS

The results obtained from the application of methods used in other studies for the isolation of pathogenic streptococci to the water supply during an epidemic of poliomyelitis and to that for a group of patients with recurring attacks of encephalomeningoradiculitis and fibromyositis are reported.

Streptococci were isolated more often from samples of water representing the central supply of the epidemic area than from water of control supplies, and much more often from water samples obtained from the very periphery where poliomyelitis occurred and where patients who had encephalomeningoradiculitis and fibromyositis were cared for. The streptococci isolated from the water supplies for the two groups of patients resembled closely the streptococci isolated directly from the patients served by the respective supplies. Each group of strains had well marked specific virulence and localizing power, demonstrated by feeding to and by injecting into animals the water shown to contain the streptococci and cultures of the streptococci. The serums of patients agglutinated specifically the respective strains of streptococci.

Isolation of streptococci on ordinary mediums usually was not possible. This inability to isolate from the water, by conventional methods, streptococci having characteristic virulence is in agreement with the fact that the usual methods often do not suffice to isolate the causative streptococci from the infected tissues of patients suffering from different diseases, especially poliomyelitis and its virus.

In agreement with epidemiologists¹⁰ and those who routinely checked the water supply, the epidemic of 1934 as a whole, judged by the usual epidemiologic criteria, almost certainly was not caused by contamination

10 Leake, J. P., Cedar, E. T., Dearing, W. P., Gilham, A. G. and Choep, H. D. Epidemiology of Poliomyelitis in California, 1934, *Am J Pub Health* 24 1204-1206 (Dec.) 1934. Stevens¹⁰

of the central water supply. The unprecedented high incidence of poliomyelitis among physicians and nurses who attended the patients and in certain family and other groups and the high incidence of recurrent attacks of encephalomeningo-radculitis and fibromyositis during and after the epidemic would seem to be attributable to the drinking water. It is considered that in acute poliomyelitis occurring during the epidemic the streptococcus was an integral part of the infectious process now generally attributed to virus and the cause of the unusual manifestations and that in the instances of encephalomeningo-radculitis with fibromyositis it was the etiologic agent unassociated with the virus. The resulting diseases, however, were certainly not mainly caused by the streptococci contained in the central water supply but may have been due to peripheral "autogenous" contamination by excreta of the persons themselves.

However, the possibility must be considered that autogenous contamination of the water by streptococci may have been from the air, for I have since isolated streptococci having specific properties from the air of rooms occupied by persons with various diseases, including poliomyelitis, and from outdoor air during epidemics.¹¹

The mere determination of the existence of back siphonage from inadequate water pressure under stress and elevation in relation to cases of the disease, according to my results, did not suffice, nor did the colon bacillus index, obtained by well established methods of water analysis from water collected from central sources. Cultures, animal inoculations and cataphoretic and serologic tests, by the methods I used, of water obtained from the very periphery were necessary to establish the presence of the respective streptococci and their specific virulence.

11 Rosenow, E. C. Isolation from the Air of Streptococci and Streptococcal Antigens Resembling Those Associated with Certain Epidemic Diseases, *J. Bact.* **39** 73-74 (Jan.) 1940.

POSTURAL HYPOTENSION

A DISEASE OF THE SYMPATHETIC NERVOUS SYSTEM

EUGENE A STEAD JR, M D

AND

RICHARD V EBERT, M D

BOSTON

Man would have syncope while standing upright if it were not for certain adaptive mechanisms which tend to maintain a constant cerebral blood flow. In the standing position the amount of blood present in the upper part of the body is decreased, first, because the vascular bed in the portion of the body below the heart is dilated by a high hydrostatic pressure¹ and, second, because the high capillary pressure causes an increased filtration of fluid from the blood stream and a decrease in plasma volume². This decrease in blood volume in the upper part of the body is compensated for by vasoconstriction and by increase in heart rate. In a group of subjects first described by Bradbury and Eggleston³ in a discussion of postural hypotension, these reactions failed to compensate for the pooling of blood and there was a striking fall in arterial pressure when the patients were in the upright position.

Observations were made on 3 patients with marked postural hypotension in order to obtain further knowledge of the physiologic mechanisms involved.

METHOD

Each of these subjects, when effects of changes in posture were to be observed, was placed on a tilt table. When the table was tilted upright most of the subject's weight rested on the feet, which were supported by an iron upright at the

From the Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School.

1 Turner, A H, Newton, M I, and Haynes, F W. Circulatory Reaction to Gravity in Healthy Young Women. Evidence Regarding Its Precision and Its Instability, *Am J Physiol* **94** 507, 1930. Grill, C. Investigations into Displacements in Blood Mass Due to Changes in Body Positions, *Acta med Scandinav* **92** 267, 1937. Asmussen, E, Christensen, E H, and Nielsen, M. Pulsfrequenz und Körperstellung, *Skandinav Arch f Physiol* **81** 190, 1939.

2 Thompson, W O, Thompson, P K, and Dailey, M E. Effect of Posture upon Composition and Volume of Blood in Man, *J Clin Investigation* **5** 573, 1928. Waterfield, R L. Effects of Posture on Circulating Blood Volume, *J Physiol* **72** 110, 1931.

3 Bradbury, S, and Eggleston, C. Postural Hypotension, *Am Heart J* **1** 73, 1925.

foot of the table. The heart rate was determined by precordial auscultation or by palpation of the radial pulse. The arterial pressure in the arm at heart level was measured with a mercury manometer by the auscultatory method.

The blood flow in the hand and in the foot was measured by plethysmographic methods.⁴ The hands and feet were in the plethysmographs at a constant temperature for at least thirty minutes before observations were begun.

The basal blood volume was determined by the method of Gibson and Evans⁵ as adapted to the photoelectric microcolorimeter.⁶ This method, combined with the application of arterial tourniquets, was used for measuring the volume of blood in the lower extremities, with the subject in the horizontal and in the standing position.⁷

REPORT OF CASES

CASE 1—A 58 year old man, an Italian laborer, was seen in July 1939. He complained of attacks of syncope when he was in the upright position. The attacks, of three years' duration, occurred infrequently, and then usually while the patient was at work. During the last six months the attacks had increased in severity and frequency, and on three occasions the patient had been injured by falling. He was unable to shave while standing because of blurred vision, tremor and syncope. Syncope was most easily produced by standing after exercise. At the onset of his difficulty the patient became impotent, and at about the same time he noted that sweating of the lower extremities had ceased. He had nocturia (urinated once each night) but had not noticed an increased output of urine at night.

Physical Examination—The subject was well developed and well nourished, appearing somewhat younger than 58. The fundi were normal. The heart was normal in size, there was a slight apical systolic murmur. The lungs and abdomen were normal. The peripheral vessels showed slight thickening. The dorsalis pedis and the posterior tibial pulsations were present. In the morning, with the subject in the horizontal position, the arterial pressure averaged 90 mm systolic and 60 mm diastolic, in the afternoon the pressure was always higher, averaging 160 mm systolic and 95 mm diastolic. With the subject in the upright position the systolic pressure rapidly fell to 50 mm of mercury or lower. The heart rate increased 30 to 40 beats per minute. If allowed to remain standing, the patient developed tremor, ataxia and finally syncope. The laboratory work showed nothing abnormal. The red blood cell count was 5,000,000. The hematocrit reading was 44 per cent. The blood urea nitrogen was 18 mg per hundred cubic centimeters. An electrocardiogram was normal. The Hinton test was negative.

Course—The subject was followed for seven months. Though he had no medication, his postural hypotension showed considerable variation. On a few occasions

4 Freeman, N. E. Effect of Temperature on Rate of Blood Flow in Normal and in Sympathectomized Hand, *Am J Physiol* **113** 384, 1935. Stead, E. A., Jr., and Kunkel, P. A Plethysmographic Method for the Quantitative Measurement of the Blood Flow in the Foot, *J Clin Investigation* **17** 671, 1938.

5 Gibson, J. G., II, and Evans, W. A., Jr. Clinical Studies of the Blood Volume. I. Clinical Application of Method Employing Azo Dye "Evans Blue" and Spectrophotometer, *J Clin Investigation* **16** 301, 1937.

6 Gibson, J. G., II, and Evelyn, K. A. Clinical Studies of Blood Volume. IV. Adaptation of Method to Photoelectric Microcolorimeter, *J Clin Investigation* **17** 153, 1938.

7 Ebert, R. V., and Stead, E. A., Jr. Effect of the Application of Tourniquets on the Hemodynamics of the Circulation, *J Clin Investigation* **19** 561, 1940.

he was able to stand for thirty minutes at an angle of 60 degrees without fainting, although his systolic pressure remained below 50 mm throughout. Aside from these spontaneous fluctuations there was no change in his condition.

CASE 2—A 56 year old man, an office worker, was seen Dec 5, 1939. He complained of weakness and dizzy spells of six months' duration. The attacks of dizziness always occurred while he was in the upright position, usually after climbing stairs or after a long walk. On two occasions he fell to the floor after getting out of bed at night. He was unable to shave while standing, because of tremor and ataxia. For the past year he had had nocturia from three to four times, with difficulty in starting his stream, and had had urinary incontinence on several occasions. His family noted some personality changes. The patient had not been conscious of any disturbance in sweating.

Physical Examination—The subject was a short, well nourished, slightly euphoric man. The pupils reacted well to light. The vessels of the fundi were normal. There was bilateral deafness of the conduction type, with no change in the tympanic membranes. The heart was not enlarged, and there were no murmurs or irregularity. The radial arteries were somewhat inelastic but not tortuous. The prostate was symmetrically enlarged and moderately firm. The deep tendon reflexes were definitely hyperactive, and the abdominal reflexes were absent. There was unsustained ankle clonus on the left. The Babinski sign was absent. There were no sensory changes. The laboratory data were: red blood cell count, 4,300,000, hemoglobin, 13.1 Gm., Wassermann and Hinton tests, negative, nonprotein nitrogen, 21 mg. per hundred cubic centimeters, urine normal, phenolsulfonphthalein excretion, 47 per cent in two hours. The residual urine was 90 to 200 cc. Lumbar puncture revealed no abnormal condition. A cystometrogram was interpreted as showing normal function of the bladder. Cystoscopic examination showed slight enlargement of the prostate with low grade cystitis. The arterial pressure with the subject in the recumbent position ranged from 98 mm. systolic and 76 mm. diastolic to 125 mm. systolic and 85 mm. diastolic, with the subject in the standing position the arterial pressure fell to 58 mm. systolic and 44 mm. diastolic. When the subject was tilted to an angle of 60 degrees on the table, the arterial pressure fell almost immediately to 50 mm. systolic and 40 mm. diastolic. The heart rate increased 15 to 20 beats per minute when he was tilted upright. The patient usually had no symptoms until systolic pressure fell below 50, then he complained of dizziness. Tremor, ataxia and finally syncope followed.

Course—The patient had a transurethral prostatectomy on Dec 20, 1939. After this he continued to have incontinence, and his postural symptoms persisted.

Though he had no medication, his postural hypotension showed considerable variation. When last seen, in March 1940, his condition was essentially unchanged.

A second cystometrogram, on May 14, revealed that the bladder was very hypertonic. After the introduction of 25 cc. of fluid into the bladder, there was decided contraction, after the introduction of 100 cc. of fluid, the contraction was accompanied with the desire to void.

CASE 3—A 72 year old man, retired printer, was seen in September 1939. He complained of attacks of syncope of two years' duration. They were characterized by blurring of vision, weakness and loss of consciousness and were precipitated by standing or exercise. Although he was never injured by falling, the attacks occurred so frequently that he was afraid to go out alone. During the last two years he had had urinary incontinence and dribbling. His memory for recent events was poor.

Physical Examination—The subject was a well preserved man, who appeared younger than his stated age. The pupils of the eyes were equal and reacted sluggishly to light. The vessels of the fundi were normal. The peripheral vessels were soft and compressible. The heart was normal in size, and there were no murmurs. The bladder was palpable above the symphysis pubis. There was moderate enlargement of the prostate. Knee jerks were present but ankle jerks were absent. There were no sensory changes. Laboratory data were: red blood cell count, 4,500,000, hemoglobin, 13.4 Gm, blood urea nitrogen, 15 mg per hundred cubic centimeters, Wassermann and Hinton tests of the blood, positive, urine normal. The spinal fluid was normal, and the Wassermann test of the spinal fluid was negative. An electrocardiogram was normal. The residual urine was 600 cc. Cystoscopic examination showed some enlargement of the median lobe of the prostate, but this was not considered sufficient to cause organic obstruction. The cystometrogram showed evidence of neurologic disease of the bladder, and this was thought to be the cause of urinary retention.

In the morning, with the patient in the recumbent position the arterial pressure averaged 90 mm systolic and 60 mm diastolic, in the afternoon the systolic pressure was between 120 and 170 mm and the diastolic between 80 and 100 mm. When the patient stood, the arterial pressure immediately fell, and in three to five minutes the systolic pressure usually was below 50 mm of mercury. When the systolic pressure fell below 40 mm, blurring of vision usually occurred. This was followed by tremor, loss of consciousness and clonic jerks of the extremities. When the patient was again placed in the horizontal position, the arterial pressure rapidly returned to the resting level, and the patient recovered consciousness. The fall in pressure did not produce any change in heart rate.

EXPERIMENTS

Effect of Motionless Standing—The arterial pressure fell rapidly when subjects were tilted upright. The heart rate remained unchanged or showed a moderate increase. There were no symptoms or signs of impaired cerebral function as long as systolic pressure did not fall below 50 mm of mercury. In certain instances systolic pressures as low as 40 mm were tolerated for ten to fifteen minutes with no apparent loss of mental acuity. The first signs of decreased cerebral blood flow were slight pallor, blurring of vision, tremor of the hands and inability to understand commands. There was no sweating or abdominal discomfort. If the motionless standing was continued, generalized clonic movements of the arms and legs without tonic spasms occurred. When the patient was returned to the horizontal position, consciousness was immediately restored and the heart rate and the arterial pressure rapidly returned to resting levels. There was amnesia relative to the events which had occurred during the latter portion of the standing period.

Effect of Application of Tourniquets on the Thighs—With the subjects lying in the horizontal position, pressure cuffs were placed on the proximal portions of both thighs and inflated suddenly from a large reservoir to a pressure of 250 mm of mercury. The subjects were then tilted to an angle of 60 to 75 degrees. The arterial pressure was main-

tained at a much higher level than without the tourniquets. For example, in case 1 after the patient stood for ten minutes with tourniquets on the thighs the arterial pressure was 106 mm systolic and 74 mm diastolic, without tourniquets the systolic pressure was always below 50 mm after he had stood for this period of time. On release of the tourniquets with the subject in the upright position, loss of consciousness and clonic movements occurred before the level of the arterial pressure could be determined. The results of these experiments agree with those reported by previous investigators⁸ and indicate that in the upright position pooling of blood in the abdomen alone does not produce a striking fall in arterial pressure.

While 1 subject was in the upright position tourniquets on the upper thighs were inflated to 250 mm of mercury after the arterial pressure had fallen below 50 mm. The subject was then returned to the horizontal position. The arterial pressure immediately rose to 120 mm systolic and 90 mm diastolic. Thus the amount of blood pooled in the extremities was not by itself sufficient to cause a fall in arterial pressure when he was returned to the horizontal position.

Effect on Postural Hypertension of External Hydrostatic Pressure—If a fall in arterial pressure is produced in cases of postural hypotension by the increased hydrostatic pressure in the vascular bed of that portion of the body below the heart, this fall should be prevented by applying external hydrostatic pressure. This was accomplished in 2 subjects by having them stand in water up to the level of the heart. With the water at the level of the heart, the arterial pressure and the heart rate were essentially the same as when the subjects were in the recumbent position. As the level of the water was lowered, arterial pressure fell progressively (chart 1). Bjure and Laurell⁹ studied a group of subjects who showed a marked rise in heart rate when they were in the upright position. When these subjects stood in water at the level of the heart there was no increase in heart rate.

Quantity of Blood in the Lower Extremities—The experiments described clearly show that pooling of blood in both the abdomen and the lower extremities is necessary to produce the drop in arterial pres-

8 (a) Allen, E. V., and Magee, H. R. Orthostatic (Postural) Hypotension with Syncope, *M. Clin. North America* **18** 585, 1934. (b) Ellis, L. B., and Haynes, F. W. Postural Hypotension, with Particular Reference to Its Occurrence in Disease of Central Nervous System, *Arch. Int. Med.* **58** 773 (Nov.) 1936. (c) Alvarez, W. C., and Roth, G. Orthostatic Hypotension. Report of Case with Some Unusual Features, *Proc. Staff Meet., Mayo Clin.* **10** 483, 1935.

9 Bjure, A., and Laurell, H. Abnormal Static Circulatory Phenomena and Their Symptoms. Arterial Orthostatic Anemia as Neglected Clinical Picture, *Upsala Lakaref. förh.* **33** 1, 1927.

sure which occurs in the upright position. In normal subjects, however, blood is pooled in the lower portion of the body on standing without the development of hypotension. The foregoing experiments do not reveal whether the fall in arterial pressure in patients with postural hypotension is the result of the pooling of a much greater amount of blood than occurs in normal subjects or is the result of an abnormal response to the pooling of the normal quantity of blood. Therefore, the quantities of blood contained in the legs in the recumbent and in the standing position were determined. The subjects with postural hypotension were tilted to an angle of 75 degrees until syncope was

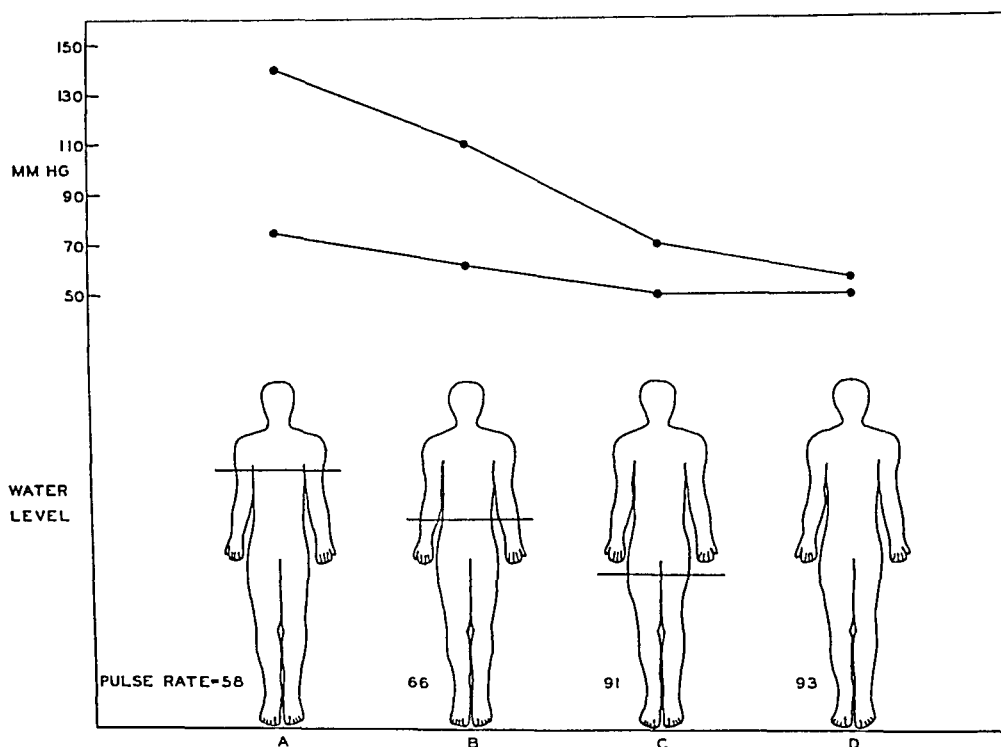


Chart 1—Effect on arterial pressure and heart rate of standing in water of various depths (case 1). In D the patient is out of the water, in A, B and C the horizontal line represents the depth of the water.

imminent, and then the arterial circulation to the legs was occluded. The normal subjects were tilted to an angle of 75 degrees for five to six minutes before the arterial circulation was occluded. The accompanying table shows the result of these experiments. In the recumbent position the lower extremities of 2 patients with postural hypotension contained 13 and 20 per cent, respectively, of the total blood volume. Under similar conditions the lower extremities of 2 normal subjects contained 13 and 19 per cent, respectively. On standing, there was no significant difference in the amount of blood pooled in the lower extremities of the subjects of the two groups. Therefore, in the subjects studied, the fall

The Amount of Blood Contained in the Lower Extremities of Two Normal Subjects and Two with Postural Hypotension

Subject	Age	Height, Cm	Weight, Kg	Diagnosis	Basal Blood Volume, Cc	Volume of Blood in Legs, Recumbent		Decrease in Volume of Blood in Upper Portion of Body on Standing		Minutes of Standing	Blood Pressure in Recumbent Position	Blood Pressure at End of Period of Standing
						Cc	Percentage*	Cc	Percentage			
C W	56	156	57	Postural hypotension	4,400	580	13	310	8	12	110/72	50/44
J P	58	177	72	Postural hypotension	5,800	1,170	20	330	7	1	135/90	65/50
J W	24	181	65	Normal	6,100	800	13	430	8	5	110/75	110/75
R E	27	172	66	Normal	5,350	1,030	19	320	7	6	121/90	108/90

* The percentage given is the percentage of the total volume of blood of the body

in arterial pressure while they were in the upright position was not the result of the pooling of an abnormal amount of blood in the lower extremities

The possibility remained that in the upright position an abnormal amount of blood was pooled in the abdomen. If this were true, the pooling of the normal amount of blood in the legs might be sufficient to overpower the normal compensatory mechanisms and produce a striking fall in blood pressure. That this is not the case was shown by experi-

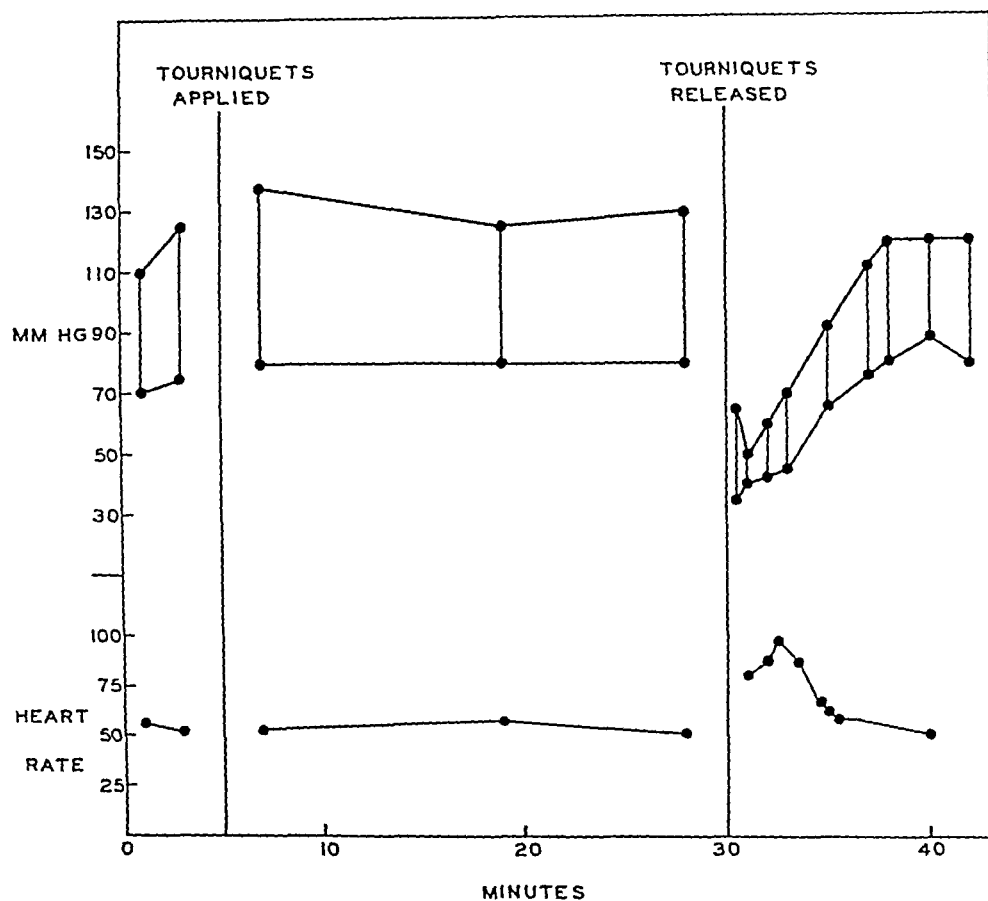


Chart 2—Effect of reactive hyperemia in the lower extremities on the arterial pressure and heart rate (case 1)

ments made with the subjects in the recumbent position, in which reactive hyperemia of the lower extremities produced a marked fall in arterial pressure when the hydrostatic pressure in the abdomen was not increased. Reactive hyperemia in the lower extremities was produced by twenty-four minute periods of arterial occlusion. On the release of the tourniquets there was a decided fall of arterial pressure with a moderate rise in heart rate (chart 2). Control observations on normal subjects in the horizontal position showed a slight and transient decrease in arterial pressure when reactive hyperemia of this degree was

produced. These observations agree with previous ones made on normal subjects¹⁰. The experiments indicate that even with the subjects in the recumbent position the removal of a quantity of blood which causes little change in a normal subject produces a striking fall in arterial pressure in patients with postural hypotension. Therefore, the primary cause of postural hypotension is not the pooling of an abnormal amount of blood but presumably an abnormal response to the pooling of a normal quantity of blood.

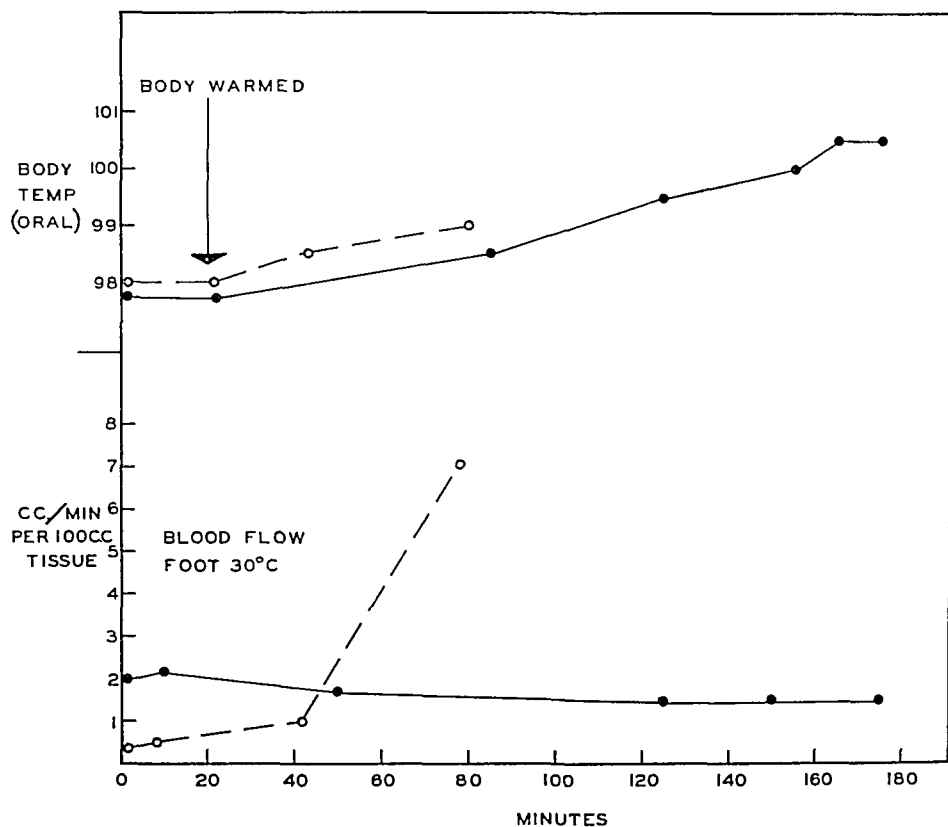


Chart 3—The effect of heating the body on the blood flow in the foot. The solid line represents case 1, the broken line, case 2.

Sympathetic Responses in Hands and Feet—When the subject of case 2 was in the recumbent position, the vasomotor reactions in the upper and lower extremities appeared normal. On pinching the skin of the body, marked vasoconstriction occurred in the hands and feet. When he was exposed in a cool room, the hands and feet became cold.

10 Jarisch, A., and Gaisbock, F. Ueber das Verhalten des Kreislaufes bei der postanämischen Hyperämie, *Arch f exper Path u Pharmacol* **139** 159, 1929.
 Asmussen, E., Christensen, E. H., and Nielsen, M. Die Effektivität der Blutdruckregulation in verschiedenen Körperstellungen, *Skandinav Arch f Physiol* **81** 204, 1939.

Heating the body caused an increased blood flow in the extremities (chart 3) and generalized sweating. Cooling the body caused the blood flow in the extremities to decrease.

When the subject of case 1 was in the recumbent position, the vasomotor reactions in the upper extremities appeared normal, but those in the lower extremities were distinctly abnormal. When he was exposed in a cool room for forty minutes, his feet remained warm (skin temperature 85 F) in spite of generalized shivering. When the body was heated from an oral temperature of 98 F to 100.5 F, there was no sweating below the ankles and very slight sweating along the anterior surfaces, of the legs and thighs. The blood flow in the hand and foot was determined with water baths at a temperature of 30 C. The body was cooled to an oral temperature of 97.9 F and then heated to 100.5 F. The flow of blood in the hand decreased and increased normally, but the flow in the foot did not change (chart 3). The temperature of the water bath surrounding the foot was then raised, and the flow of blood immediately increased, indicating that the blood vessels responded normally to local changes in temperature. In case 3 these studies were not made, but it was noted that the subject's hands and feet became cold when the body was exposed in a cool room and that sweating in the hands was normal when the body was warm. The sweating reaction in the feet was not studied.

Effect of Standing on Blood Flow of the Hand—When the subject was in an upright position, the vessels of the hands did not constrict normally to a fall in arterial pressure, although the studies with the subject in the horizontal position had shown that the peripheral sympathetic nerves supplying the vessels of the hand were intact. Chart 4 shows the effect on the blood flow in the hand at 37 C (98.6 F) produced by tilting the subject of case 2 to an angle of 40 to 75 degrees above the horizontal. As the arterial pressure fell, the blood flow decreased but never fell below 6 cc per minute per hundred cubic centimeters of hand. A similar result was obtained in case 1. In normal subjects with a smaller sudden fall in blood pressure, the blood flow in the hands was nearly zero.

Effect of Blood Transfusion—In postural hypotension, in the absence of the usual compensatory reactions the increased hydrostatic pressure produced when the patient is in the upright position causes the vascular bed to be too large to be adequately filled by the normal blood volume. If this volume were increased and the vascular system filled, the blood pressure should be maintained with the subject in the upright position. Chart 5 shows the effect of giving 1,000 cc of blood to the patient described in case 1. He was tilted to an angle of 20 degrees, this was

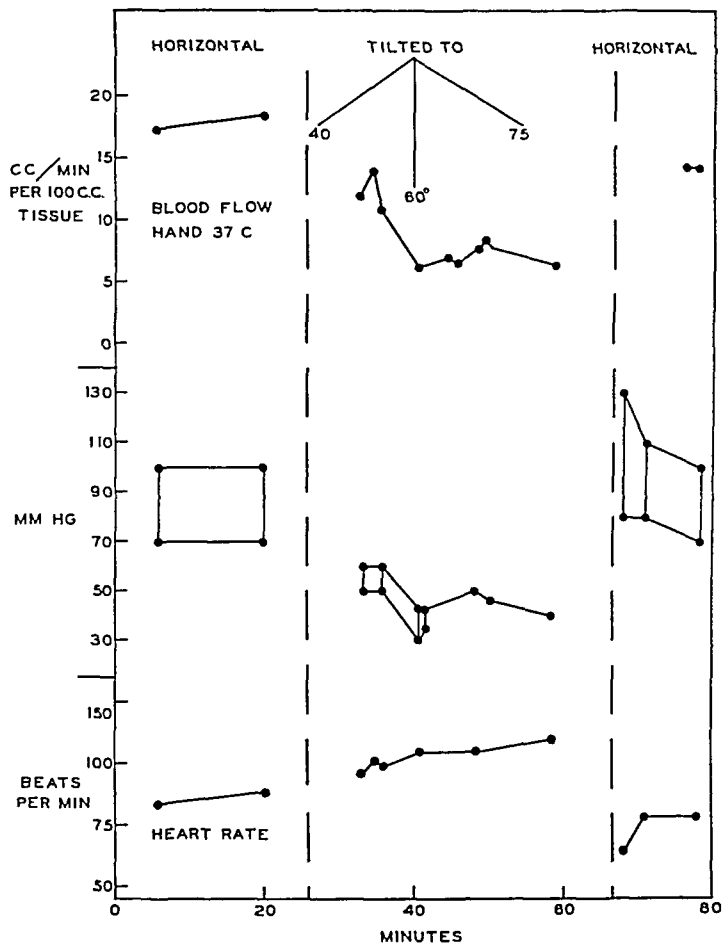


Chart 4—The effect of the upright position on the arterial pressure, the heart rate and the blood flow in the hand (case 2)

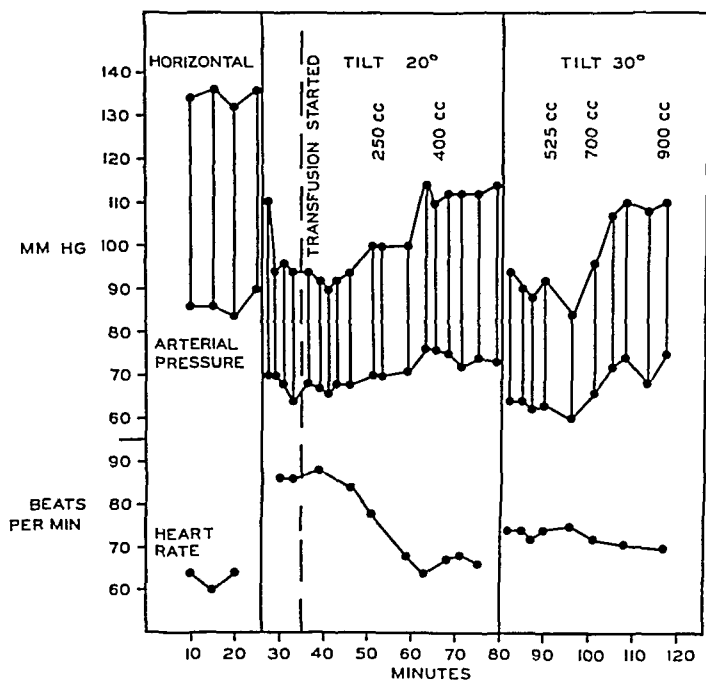


Chart 5—The effect of transfusion on the arterial pressure and the heart rate (case 1)

sufficient to cause a fall in arterial pressure and a rise in pulse rate. Then the transfusion was started. The arterial pressure rose and the pulse rate fell. The subject was then tilted to an angle of 30 degrees, this again caused the arterial pressure to fall. The transfusion was continued, with a second rise in arterial pressure.

COMMENT

The cardiovascular reactions of subjects with postural hypotension differ in several respects from those of normal subjects whose postural adaptations have been temporarily deranged, by sodium nitrite,¹¹ by acute infections or by loss of blood.¹² The fall in systolic and diastolic pressure before the onset of symptoms is more rapid and much greater than that seen in other types of postural fainting, in the latter the diastolic pressure tends to be fairly well maintained until just before the onset of syncope, although the pulse pressure is very low. The heart rate in postural hypotension is unchanged or shows a moderate increase as the arterial pressure falls. This increase is usually not as great as that which occurs in normal subjects during the early part of postural collapse. Subjects with postural hypotension remain symptom free while standing, as long as the systolic pressure remains as high as 50 mm of mercury, normal persons are frequently uncomfortable if the pressure is lowered from 120 to 90 mm of mercury, and marked symptoms usually develop when the systolic pressure falls to 80 or 70 mm. Syncope occurs in subjects with postural hypotension without the extreme pallor, nausea, sweating and slow pulse rate which usually characterize other types of postural fainting. The onset of syncope is therefore not unpleasant, and subjects do not object to its repeated production.

Each of 3 subjects studied noted that the attacks of syncope which they experienced when in the upright position were precipitated by exercise, particularly by walking upstairs. Exercise causes vasodilation in the vascular bed of the muscle, so that the extremities hold more blood. Normal subjects may faint if they stand motionless after short but strenuous exercise,¹³ in persons with postural hypotension, moderate exercise without motionless standing may produce symptoms.

In cases 1 and 3 the attacks of syncope were much more frequent in the morning than in the afternoon. In the morning, with the subjects resting recumbent, their arterial pressure was around 100 mm systolic

11 Weiss, S., Wilkins, R. W., and Haynes, F. W. The Nature of Circulatory Collapse Induced by Sodium Nitrite, *J. Clin. Investigation* **16** 73, 1937.

12 Stead, E. A., Jr., and Ebert, R. V. Unpublished data.

13 Mateeff, D. Der orthostatische Kreislaufkollaps—Gravitationsschock (Gravity-Shock) beim Menschen nach körperlicher Arbeit, *Arbeitsphysiol.* **8** 595, 1935.

and 60 mm diastolic, when they stood, the pressure rapidly fell to syncopal level. In the afternoon the subjects frequently had definite hypertension while they were in the recumbent position (systolic pressure around 160 mm), and though the pressure began to fall immediately when they stood, it did not reach the syncopal level as quickly as in the morning. The significance of this decided rise in pressure in the afternoon is not understood. In interpreting the results of any medication this variation must be remembered.

In postural hypotension there is a fall in arterial pressure when the patient is in the upright position because normal vasoconstriction does not occur when blood is pooled in the portion of the body below the heart. It is not produced by a small total blood volume or by the pooling of an abnormal amount of blood as a result of increased hydrostatic pressure. The absence of normal vasoconstriction in response to a fall in arterial pressure is shown by the following observations: (a) There is a marked drop in diastolic pressure when the patient is in the upright position, (b) marked pallor does not occur, (c) the shunting of a given amount of blood into the extremities produces a much greater fall in arterial pressure in patients with postural hypotension than in normal subjects, (d) for a given decrease in arterial pressure the blood flow in the hand is much higher than that in normal subjects, and (e) other investigators^{8b} have demonstrated that the fall in arterial pressure is not accompanied by a great decrease in cardiac output.

The absence of vasoconstriction in other parts of the body when the vascular bed in one part of the body is dilated is the essential feature that distinguishes the clinical syndrome of postural hypotension from that of other types of poor postural adaptation. The absence of the postural vasoconstriction reflex, however, is frequently accompanied by a tendency to a fixed heart rate,¹⁴ by disturbances in sweating¹⁴ and by impotence,¹⁴ it is less frequently accompanied by loss of reflex vasoconstriction and vasodilation in response to changes in body temperature¹⁵ and by disturbances in the function of the bladder.¹⁶

This failure of vasoconstriction in response to a fall in blood pressure could result from (a) loss of intrinsic tone in the capillaries and

14 Chew, E. M., Allen, E. V., and Barker, N. W. Orthostatic Hypotension. Report of Six Cases and Review of the Literature, *Northwest Med* **35** 297, 1936. Bradbury and Eggleston.³

15 MacLean, A. R., and Horton, B. T. Myasthenia Gravis with Postural Hypotension, *Proc. Staff Meet., Mayo Clin* **13** 21, 1938. Alvarez and Roth.^{8c}

16 Ganshorn, J. A., and Horton, B. T. Postural Hypotension. Report of Case, *Proc. Staff Meet., Mayo Clin* **9** 541, 1934. Baker, T. W. Recognition of Orthostatic Hypotension. Report of Case, *ibid* **13** 169, 1938.

arterioles or (*b*) interference with the reflexes which regulate the arterial pressure. There is evidence that the arterioles and the capillaries were functioning normally when properly stimulated, because heat applied locally caused vasodilatation in the vessels of the extremities and cold applied locally caused vasoconstriction.

Postural hypotension in these subjects is therefore a disease of the nervous system, in which the reflexes that control the level of the arterial pressure do not function properly.

Theoretically, the disease could result from (*a*) lesions in the afferent receptors of the carotid bulb and the aorta, (*b*) lesions involving the spinal efferent tracts, (*c*) lesions in the sympathetic ganglions or nerves and (*d*) lesions in the autonomic centers in the central nervous system.

There is considerable evidence that postural hypotension is not the result of lesions in the afferent receptor system, although it has been demonstrated that postural changes in blood pressure develop in dogs after destruction of the carotid sinus and the aortic depressor nerve.¹⁷ A disturbance in this portion of the postural reflex arc might cause the lack of vasoconstriction in response to a fall in arterial pressure, but it would not produce the disturbances in sweating, in the regulation of temperature and in the function of the bladder which are frequently seen in this disease. Ellis and Haynes^{8b} found that in postural hypotension pressure on the carotid sinus produced a fall in arterial pressure and that the carotid sinus responded normally when stimulated by cyanide.

It has been demonstrated that lesions in the spinal cord which break the spinal efferent limb of the postural reflex arc may produce postural hypotension. Ellis and Haynes^{8b} reported a case in which postural hypotension developed after trauma to the upper dorsal part of the spinal cord. There is no indication that in the cases reported here the disease was caused by lesions in the spinal cord.

It has been suggested that the fundamental disturbance may be in the peripheral sympathetic nervous system,¹⁸ since many of the subjects with postural hypotension have shown disturbances in sweating and in cardiac acceleration as well as failure of the blood vessels to constrict when the arterial pressure is lowered. This view is supported by the fact that extensive resection of the peripheral sympathetic system produces postural hypotension. Marked postural changes in arterial pressure have been produced in hypertensive subjects by extensive

17 Hering, H. E. Ueber die Blutdruckregulierung bei Änderung der Körperstellung vermittels der Blutdruckzugler und das Zustandekommen der Ohnmacht beim plotzlichen Uebergang vom Liegen zum Stehen, München med. Wchnschr. 74 1611, 1927.

18 Bradbury and Eggleston³ Alvarez and Roth^{8c} Chew, Allen and Barker¹⁴

sympathectomy¹⁹ (resection of the splanchnic nerves and removal of the lower portions of the sympathetic chains) Animals which have been totally sympathectomized also show a resemblance to the patients with postural hypotension in their failure to compensate for sudden changes in blood volume Schlossberg and Sawyer²⁰ reported that a small hemorrhage in a normal cat produces only a transient fall in blood pressure, whereas a similar hemorrhage in a sympathectomized animal produces a lasting fall in pressure Completely sympathectomized dogs tolerate a low blood pressure better than normal dogs, and for a given level of blood pressure the peripheral blood flow is greater in the sympathectomized animals than in normal ones²¹

Postural hypotension can be produced by destruction of the peripheral sympathetic nerves and ganglions¹⁹ and by extensive damage to the spinal cord^{8b} The studies reported here show that the clinical cases in which postural hypotension develops in the absence of operative procedures and without extensive lesions in the spinal cord are characterized by a disturbance in the function of the sympathetic nervous system It remains to be decided whether this disturbance is in the peripheral sympathetic system or in the central connections of the sympathetic system In the cases presented, the data indicate that the disease is probably in the central nervous system This conclusion is based on the assumption that all the efferent impulses for vasoconstriction have a common pathway below the sympathetic ganglions If this is true, then lack of vasoconstriction in the hands in response to a fall in arterial pressure could not have been caused by destruction of the postganglionic fibers or their nerve cells, because these nerves were intact, as demonstrated when vasoconstriction was produced in the hands by cooling the body and by pinching the skin It is also improbable that in case 2 a disturbance in the sympathetic ganglions or nerves would have produced such widespread loss of reflex control of blood pressure without causing other demonstrable signs of involvement of the sympathetic system The absence of sweating and the disturbance of reflex heat control in case 1 can be accounted for equally well by lesions in the peripheral sympathetic or lesions in the central nervous system The observations of Ellis and

19 (a) Allen, E V, and Adson, A W Physiologic Effects of Extensive Sympathectomy for Essential Hypertension Further Observations, *Ann Int Med* **11** 2151, 1938 (b) Smithwick, P Technique for Splanchnic Resection for Hypertension, *Surgery* **7** 1, 1940

20 Schlossberg, T, and Sawyer, M E M Studies of Homeostasis in Normal, Sympathectomized and Ergotaminized Animals Effect of Hemorrhage, *Am J Physiol* **104** 195, 1933

21 Freeman, N E, Shaffer, S A, Schechter, A E, and Holling, H E Effect of Total Sympathectomy on Occurrence of Shock from Hemorrhage, *J Clin Investigation* **17** 359, 1938

Haynes^{8b} support the conclusion that postural hypotension is produced by disease of the central nervous system. They point out that in many of the cases described in the literature there have been other signs of disease of the central nervous system. Ten of the 17 patients with *tabes dorsalis* whom these authors studied had an abnormal fall in blood pressure when standing.

Lesions in the spinal cord, the medulla or the hypothalamus can disturb the functions of the sympathetic nervous system. If lesions in the spinal cord are responsible for the disease, they must be high enough to involve the hands, because the normal vasoconstriction in the hands does not occur in response to a fall in blood pressure. The efferent pathways in the spinal cord and medulla have not been studied extensively, and it is not known to what extent dissociation of sympathetic functions can be produced by lesions of the efferent sympathetic tracts or of their connections. The different portions of the sympathetic system do not appear to be widely separated in the medulla, because stimulation of a small area in the medulla may call forth a number of sympathetic reflexes.²²

On the basis of animal experiments it has been shown that lesions in the hypothalamus are more apt to produce disturbances in one portion of the sympathetic system without producing complete destruction of sympathetic function.²³ A lesion in the hypothalamus could produce the disturbances in sweating and the partial loss of reflex heat control observed in the subjects described. It could also account for the disturbances of the bladder function. It is not known, however, whether lesions in the human hypothalamus could produce the loss of the postural blood pressure reflex.

If postural hypotension in the cases reported here is a disease of the central nervous system, the experiments indicate that central lesions of the sympathetic nervous system produce signs that are different from those caused by removal of the sympathetic ganglions or nerves, just as lesions in the sensory cortex produce signs that differ from those caused by sectioning the posterior roots. When the sympathetic nerves to an extremity are sectioned, all sympathetic reflexes are lost. The cases reported here show that a selective disturbance in sympathetic function may occur. Reflexes which have a common efferent pathway in the peripheral sympathetic system are controlled by different areas in the central nervous system. One vasoconstrictor reflex (vasoconstriction in

22 Chen, M. P., Lim, R. K. S., Wang, S. C., and Yi, C. L. On the Question of a Myelencephalic Sympathetic Center. I. The Effect of Stimulation of the Pressor Area on Visceral Function. *Chinese J. Physiol.* **10**: 445, 1936.

23 Ransom, S. W., and Magoun, H. W. The Hypothalamus, *Ergebn. d. Physiol.* **41**: 56, 1939.

response to a fall in arterial pressure) may be destroyed while other vasoconstrictor reflexes to the same extremity (vasoconstriction in response to cooling the body and to pinching the skin) are functioning. It would also appear that in man other sympathetic reflexes, i.e., cardiac acceleration to a fall in arterial pressure, vasodilatation and vasoconstriction to changes in body temperature and sweating, may be selectively affected by lesions in the central nervous system.

SUMMARY AND CONCLUSIONS

Patients with postural hypotension do not pool more blood in the lower part of the body on standing than do normal subjects under similar conditions. The pooling of the normal amount of blood causes an abnormal fall in blood pressure. The reflex vasoconstriction, which maintains the arterial pressure in normal subjects under similar conditions, does not occur in patients with postural hypotension. This loss of reflex vasoconstriction in response to a fall in arterial pressure is the fundamental disturbance in postural hypotension and distinguishes it from other types of poor postural adaptation.

Postural hypotension is a disease of the sympathetic nervous system. It cannot be definitely stated whether the involvement of the sympathetic system is peripheral or central. The observations reported in this study point to the interpretation that the lack of vasoconstriction in response to a fall in arterial pressure is produced by a lesion or lesions in the sympathetic centers or their efferent tracts in the central nervous system rather than by lesions in the more peripheral portions of the postural blood pressure reflex arc. In certain patients only the postural vasoconstrictor reflexes are affected. If the lesions are more extensive, other signs of loss of sympathetic function may be present, such as disturbances in sweating, absence of vasoconstriction and vasodilatation in the extremities when the temperature of the body is changed and absence of an increase in heart rate when the blood pressure is lowered.

Dr. Soma Weiss gave guidance and criticism in this work. Miss Blanche Curtis gave technical assistance.

ALUMINUM PHOSPHATE IN THE THERAPY OF PEPTIC ULCER

EFFECT OF ALUMINUM HYDROXIDE ON PHOSPHATE ABSORPTION

G. B. FAULEY, M.D.

SMITH FREEMAN, M.D., Ph.D.

A. C. IVY, M.D., Ph.D.

A. J. ATKINSON, M.D.

AND

H. S. WIGODSKY, M.S.

CHICAGO

Our use of an aluminum phosphate gel in the therapy of peptic ulcer resulted from observations on the effect of aluminum hydroxide gel on the absorption of phosphates from the intestine. In a publication¹ on the effect of aluminum hydroxide gel on the well-being and longevity of Mann-Williamson dogs, Fauley, Ivy, Terry and Bradley suggested that the unfavorable effects of this chemical in such animals might be due to an interference with the absorption of phosphates. The present report (a) includes data which demonstrate that aluminum hydroxide gel interferes with phosphate absorption and (b) presents the results of the use of aluminum phosphate gel in the treatment of experimental and clinical peptic ulcer.

Experimental ulcers were produced in Mann-Williamson dogs. The preparation of such an animal includes performing a gastrojejunostomy and diverting the pancreatic juice and bile into the terminal portion of the ileum (last 20 to 25 cm.). Of 42 dogs so operated on and fed a diet of meat, bread, milk and cod liver oil (8 cc. daily), jejunal ulcer developed in all and all died in seventeen weeks (average, eleven weeks). This experimentally induced ulcer is analogous to the ulcer that sometimes occurs after gastrojejunostomy in man. The diversion of pancreatic juice and bile to the terminal portion of the ileum in the dog markedly increases the incidence of jejunal ulcer. Much experimental

From the Department of Physiology and Pharmacology, Northwestern University Medical School.

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1. Fauley, G. B.; Ivy, A. C.; Terry, L. and Bradley, W. B.: An Attempt to Prevent Post-Operative Jejunal Ulcer by Aluminum Hydroxide Therapy, *Am. J. Digest. Dis.* 5:792 1939.

work has shown that at least three factors are concerned in the development of this experimental ulcer,² the most important one is the acid factor, another is the nutritional factor, since the diversion of pancreatic juice and bile to the lower part of the ileum disturbs intestinal digestion, as well as the neutralization of acid chyme, and the third factor is the increased sensitivity of the jejunal mucosa to gastric chyme as compared with that of duodenal mucosa.

When aluminum hydroxide was given to Mann-Williamson dogs, either four times daily or at hourly intervals from 8 a. m. to 8 p. m., with complete control of gastric acidity for that period, the development of ulcers was not prevented.¹

After these animals received aluminum hydroxide for three or four weeks anorexia developed. It was thought that the anorexia might counteract any beneficial effect the aluminum hydroxide gel might otherwise exert. Since anorexia is a conspicuous symptom of phosphorus deficiency³ and since soluble aluminum compounds in the diet may produce rickets and a low level of phosphorus in the blood,⁴ it seemed probable that these animals had a phosphorus deficiency.

ALUMINUM HYDROXIDE AND PHOSPHORUS METABOLISM

The following data demonstrate the effect of aluminum hydroxide on the absorption of phosphates from the intestine. The preparation of aluminum hydroxide was the same as that used in previous studies.⁵

2 (a) Ivy, A. C., and Fauley, G. B. Factors Concerned in Determining the Chronicity of Ulcers in the Stomach and Upper Intestine, *Am J Surg* **11** 531, 1931. (b) Fauley, G. B., and Ivy, A. C. The Prevention of Post-Operative Jejunal Ulcers by Diet and Fundusctomy, *Surg, Gynec & Obst* **63** 717, 1936. (c) Morton, C. B. Observations on Peptic Ulcer, *Ann Surg* **85** 207, 229 and 879, 1927. (d) Orndorff, J. R., Fauley, G. B., and Ivy, A. C. The Prophylactic Value of Gastric Mucin in the Therapy of Post-Operative Jejunal Ulcer. An Experimental Study, *Am J Digest Dis* **3** 26, 1936. (e) Mathews, W. B., and Dragstedt, L. B. The Etiology of Gastric and Duodenal Ulcers, *Surg, Gynec & Obst* **55** 265, 1932. (f) McCann, J. C. Experimental Peptic Ulcer, *Arch Surg* **19** 600 (Oct) 1929.

3 Kleiber, M., Goss, H., and Guilbert, H. R. Phosphorus Deficiency Metabolism and Food Utilization in Beef Heifers, *J Nutrition* **12** 121, 1936.

4 Cox, G. J., Doods, M. L., Wigman, H. B., and Murphy, F. J. The Effect of High Doses of Aluminum and Iron on Phosphorus Metabolism, *J Biol Chem* **92** 11, 1931. Jones, J. H. The Metabolism of Calcium and Phosphorus as Influenced by the Addition of Salts of Metals Which Form Insoluble Phosphates, *Am J Physiol* **124** 230, 1938. Deobald, H. J., and Elvehjem, C. A. The Effect of Feeding High Amounts of Soluble Iron and Aluminum Salts, *ibid* **111** 118, 1935. McKenzie, K. The Biochemistry of Aluminum, *Biochem J* **24** 1433, 1930, **25** 287, 1931.

5 Ivy, A. C., Terry, L., Fauley, G. B., and Bradley, W. B. The Effect of Administration of Aluminum Preparations on the Secretory Activity and Gastric Acidity of the Normal Stomach, *Am J Digest Dis* **3** 879, 1937.

The Effect of Aluminum Hydroxide Gel on the Excretion of Phosphorus in the Urine and Feces of Dogs—The data in table 1 show definitely that aluminum hydroxide gel given to normal dogs decreases the excretion of phosphorus in the urine and increases the excretion of phosphorus in the feces. They illustrate further that when a diet adequate in phosphorus and calcium is fed phosphorus is retained in the body, but that when aluminum hydroxide in relatively large doses is administered with such a diet no phosphorus is retained. However,

TABLE 1—*Effect of Aluminum Hydroxide Gel on Excretion of Phosphorus in the Urine and Feces of Dogs*

Dog No	Procedure	Average, 3 Day Periods			Comment	Dog No	P in 3 Day Sample of Urine, Gm
		Urinary P, Gm	Fecal P, Gm	Total P, Gm			
Diet A,* Containing 3.9 Gm of P and 3.6 Gm Ca in 3 Days							
1†	No Al(OH) ₃	1.18	1.61	2.79	P retained 0.44 Gm	3	1.08
		1.33	2.40	3.73			1.08
		1.21	2.72	3.93			
		1.47	1.91	3.38			
	Average	1.30	2.16	3.46			1.08
	With 130 cc 5% Al(OH) ₃	0.48	3.48	3.96	No P retained	3	0.68
0.29	4.70	4.99	0.32				
0.37	2.96	3.33					
Average	0.38	3.71	4.09			0.50	
Diet B, Containing 3.0 Gm of P and 0.246 Gm Ca in 3 Days							
2	No Al(OH) ₃	1.34	0.42	1.76	P retained 0.5 Gm	4	2.34
		2.56	0.46	3.02			2.56
		1.44	0.47	1.91			2.10
		2.54	0.76	3.30			2.08
	Average	1.97	0.53	2.50			2.27
	With 130 cc 5% Al(OH) ₃	0.78	1.53	2.31	P retained 0.57 Gm	4	0.65
0.57	1.21	1.78	0.65				
1.32	2.07	3.39	0.85				
0.64	1.20	1.84					
	0.91	1.95	2.86				
Average	0.84	1.59	2.43			0.72	

* Diet A contained meat, cereal, vitamins and bone meal, diet B contained beef hearts alone.

† Dog 1, on diet A, illustrates the effect of aluminum plus calcium on the diminution of phosphorus absorption, dog 2, on diet B, illustrates the effect of aluminum alone.

when the diet is lean meat, aluminum hydroxide gel in the dose used does not materially disturb the retention of phosphorus. It may be concluded that when an ordinary diet is fed aluminum hydroxide gel interferes with the absorption of phosphates in the dog.

The Influence of Aluminum Hydroxide Gel on the Urinary Excretion of Phosphorus in the Normal Adult Human Subject Receiving a "Light Ulcer Diet"—Four men were placed on a "light ulcer diet" containing approximately 2 Gm of phosphorus and 2 Gm of calcium daily. They took the diet for twelve days. During the first five days no aluminum was administered, and an average of 1.1 Gm of phosphorus was excreted.

daily in the urine (table 2) During the next seven days a total of 240 cc of a 5 per cent aluminum hydroxide gel, divided into three doses, was consumed daily with the meals, and an average of 0.44 Gm of phosphorus was excreted daily. Thus, the dose of aluminum hydroxide used reduced the excretion of phosphorus in the urine an average of 60 per cent when a light ulcer diet relatively high in phosphorus (2 Gm) and calcium (2 Gm) was ingested.

The Influence of Aluminum Hydroxide Gel on Urinary and Fecal Excretion of Phosphorus in a Child with Marble Bone Disease on a Low Phosphorus Diet—A 5 year old child with marble bone disease was placed on a low phosphorus diet accompanied by aluminum hydroxide therapy with the idea that the progress of the disease might at least

TABLE 2—*Influence of Aluminum Hydroxide Gel on the Urinary Excretion of Phosphorus in Normal Adult Subjects Receiving a Light Ulcer Diet**

Day	Subject, Gm P per 24 Hr				Comment
	1	2	3	4	
1	0.56	1.26	0.96	0.78	Diet alone containing 2 Gm P by calculation
2	0.95	1.24	1.69	0.92	
3	1.19	1.53	1.15	1.08	
4	1.01	0.99	1.09	1.01	
5	1.13	0.98	1.13	1.37	
Average	0.97	1.20	1.20	1.03	1.10
6	0.68	0.87	0.73	0.66	Diet plus 240 cc of 5% Al(OH) ₃
7	0.36	0.60	0.45	0.30	
8	0.40	0.53	0.42	0.29	
9	0.38	0.51	0.85	0.34	
10	0.39	0.37	0.28	0.28	
11	0.25	0.28	0.64	0.13	
12	0.12	0.35	0.62	0.27	
Average	0.37	0.51	0.57	0.32	0.44

* Whole milk, 1,000 cc 18 per cent cream 400 cc, butter 50 Gm white bread, 60 Gm gelatin, 100 Gm (dry weight), orange juice, 100 cc, chicken, 60 Gm, dry cereal, 20 Gm, and potatoes, 200 Gm

be retarded. Patients with this disease have an extraordinary tendency to retain phosphorus. Inspection of the data in table 3 shows that the child on the low phosphorus diet retained phosphorus even when 4 cc of a 5 per cent aluminum hydroxide gel was given four times daily. When the dose of aluminum hydroxide was increased to 30 cc four times daily the phosphorus balance became negative. The results show that even in marble bone disease a negative phosphorus balance may be produced by aluminum hydroxide when the diet is low in phosphorus.

The Extraction of Phosphorus from the Intestinal Mucosa by a Mixture of Aluminum Hydroxide Gel and Hydrochloric Acid—The following typical protocol of an experiment illustrates that in the absence of bile and pancreatic juice a mixture of 5 per cent aluminum hydroxide gel and tenth-normal hydrochloric acid extracts phosphorus from the

body fluids A A cannula was inserted and the small intestine was irrigated with warm physiologic solution of sodium chloride B Two hours later the intestine was again irrigated and the solution analyzed for phosphorus, 3.62 mg of phosphorus was obtained C A mixture of 100 cc of 5 per cent aluminum hydroxide and 200 cc of tenth-normal hydrochloric acid was introduced into the intestine D Two hours later the mixture was removed and the intestine was irrigated with warm physiologic solution of sodium chloride Forty-one milligrams of phosphorus was obtained When 100 cc of a 5 per cent aluminum hydroxide gel alone was used 16 mg of phosphorus was obtained

TABLE 3—*Influence of Aluminum Hydroxide Gel on Urinary and Fecal Excretion of Phosphorus in a Five Year Old Child with Marble Bone Disease on a Low Phosphorus Diet**

Phosphorus Intake 0.2 Gm Daily, or 1.0 Gm in 5 Days

Five Day Periods	Phosphorus in Gm for 5 Day Period			Procedure, Phosphorus Retention
	Urine	Feces	Total	
1	0.55	0.31	0.86	Low P diet, 1 Gm in 5 days
2	0.55	0.14	0.69	
Average	0.55	0.225	0.775	P retention, 0.225 Gm
1	0.35	0.55	0.90	Low P diet plus 1 drachm (3.7 cc) 5% $\text{Al}(\text{OH})_3$ q i d
2	0.18	0.99	1.17	
3	0.044	0.60	0.644	
Average	0.191	0.71	0.901	P retention, 0.1 Gm
1	0.011	1.40	1.411	Low P diet plus 1 ounce (29.57 cc) 5% $\text{Al}(\text{OH})_3$ q i d
2	0.006	1.70	1.706	
Average	0.0085	1.55	1.558	P loss, 0.558 Gm

* Dr W. M. Clifton and the staff of the Children's Memorial Hospital cooperated in the metabolic study on the child with marble bones.

These results show that aluminum hydroxide alone or a mixture of aluminum hydroxide and aluminum chloride in the intestines in sufficient concentration may extract phosphorus from the mucosa.

Comment—The results of the foregoing experiments show, as might be predicted, that aluminum hydroxide interferes with the absorption of phosphates and under certain conditions can cause a negative phosphorus balance. A phosphorus deficiency is not to be expected until the soluble aluminum salts, aluminum chloride for example, are in excess of one-half the total phosphorus in the diet. When this obtains in rats, chicks, guinea pigs and rabbits, the inorganic phosphorus in the blood is likely to be reduced.⁴ Conditions that would predispose to the development of a negative phosphorus balance on aluminum hydroxide gel therapy are not likely to be present for a prolonged period in the patient with ulcer. The ordinary ulcer diets contain adequate phosphorus. Still the

possibility has to be considered, and it should be carried in mind that anorexia, though not pathognomonic of phosphorus deficiency, is a conspicuous symptom of this condition

In order to test aluminum hydroxide therapy under controlled conditions in laboratory animals, the experimental conditions should simulate as closely as possible the actual conditions in man, otherwise the results apply only to the experimental animals and cannot be applied interpretatively to man. In the Mann-Williamson dog a postoperative jejunal ulcer develops when the alkaline juices enter the lower part of the ileum. This renders the Mann-Williamson dog more susceptible to the production of a phosphorus deficiency by aluminum hydroxide gel than a patient, unless the patient has a gastroenterostomy associated with a high grade deficiency of pancreatic juice and bile, or has relative hypersecretion of gastric juice, which will change much of the aluminum hydroxide gel into aluminum chloride. Aluminum hydroxide forms aluminum chloride on reacting with hydrochloric acid, and the aluminum chloride will react with soluble phosphate to form insoluble aluminum phosphate. The absence of the alkaline pancreatic juice from the upper part of the intestine might favor the formation of aluminum phosphate, since the aluminum would probably exist longer in the form of the chloride rather than undergo rapid conversion to the less reactive, insoluble aluminum hydroxide. Further, the Mann-Williamson dog, like some patients with jejunal ulcer, usually has an increased rate of passage through the alimentary canal and loose stools, which predisposes to an inadequate absorption of minerals.

In view of the foregoing considerations, it was pointed out in the paper by Fauley, Ivy, Terry and Bradley¹ that their results with aluminum hydroxide gel in the Mann-Williamson dog are not necessarily applicable to the ordinary human patient with peptic ulcer. It should also be evident that in order to test the theoretic therapeutic advantages of "aluminum" therapy in our experimental animals, it would be necessary to use an aluminum phosphate gel.

PREVENTION AND HEALING OF ULCER WITH ALUMINUM PHOSPHATE GEL

The Aluminum Phosphate Gel Used—The aluminum phosphate was prepared in the form of a gel by precipitating aluminum chloride with dibasic sodium phosphate (Na_2HPO_4), adjusting the p_{H} , washing free of salt and adjusting the gel to a concentration by chemical analysis, of 4 Gm of aluminum phosphate per hundred cubic centimeters of solution.⁶ The p_{H} of the gel used was about 6.5. One hundred cubic centimeters of the 4 per cent gel buffered 100 cc of tenth-normal hydrochloric acid at

6 The gel was prepared in quantity for us by Wyeth & Brother, Inc.

37 C, a p_H of 4.0 (Topfer's indicator) being used as the end point of the titration. More accurately, 30 cc, or 2 equivalents, of the gel raises the p_H of 150 cc of tenth-normal hydrochloric acid from 1.0 to 2.4. The antacid value of the 4 per cent aluminum phosphate gel (4 per cent aluminum phosphate) is slightly less than one-half that of the 4 per cent aluminum hydroxide gel (4 per cent aluminum oxide, Al_2O_3). The antacid value of various compounds is shown in figure 1.

The administration of 120 cc daily of the aluminum phosphate gel to 2 dogs caused a slight increase in the urinary excretion of phosphates.

Prevention of Ulcer—Both the treated and the control animals received a daily diet consisting of 200 Gm of raw ground pancreas,

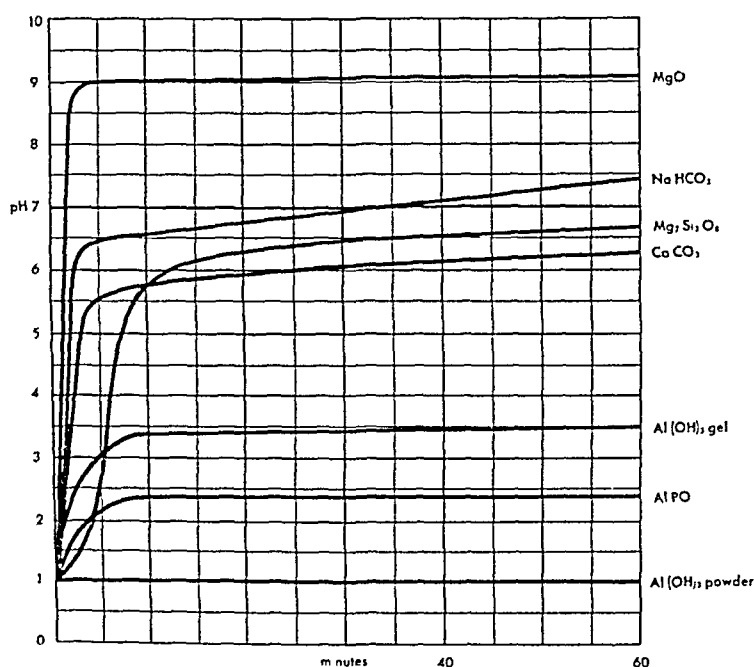


Fig 1—Reaction rate of 2 equivalents of various antacids and 150 cc of tenth-normal hydrochloric acid at 37 C with stirring and use of the glass electrode

200 Gm of raw ground liver, 100 cc of milk, 450 Gm of a commercial dog food (diet A) and 8 cc of cod liver oil. The diet was fed ad libitum twice daily, at 9 a m and 4 p m.

Sixteen control animals died with ulcer in from two to five months after the operation (Mann-Williamson, with an end to side anastomosis), the average time of survival being seventeen weeks.

Twenty-three treated animals received 100 cc of the aluminum phosphate at 7 a m, 12 noon, 5 p m and 10 p m. Ulcer developed in only 3, or 13 per cent, of the animals. If one omits the 3 animals which died without ulcer under five months, then ulcer developed in 3, or 15 per cent, of 20 animals (table 4).

Comment—This is a striking result, the best that we have obtained with any therapy.

Healing of Ulcer—The aluminum phosphate therapy was discontinued in the case of 2 animals in which an ulcer had not developed (verified by exploration) ten months after the Mann-Williamson operation. Loss in weight and tarry stools developed in 1 of these animals in nine weeks, and in the other in fourteen weeks. On restoration of therapy, the ulcer was found (by exploration) to be healed in sixteen weeks in the first dog and in eleven weeks in the second dog. This procedure was repeated twice on the same dogs. With the third recurrence of ulcer on withdrawal of aluminum phosphate, the ulcer was found healed in four weeks (etherization and autopsy) in 1 dog and in

TABLE 4—Results of the Use of Aluminum Phosphate Gel on Mann-Williamson Dogs

No. of Dogs	Time in Months	Ulcer	Cause of Death
16 control animals	2 to 5, average 17 weeks	All	
Twenty Three Animals Treated with AlPO_4			
3 animals dying with ulcer *	2, 5, 5, 9	All	Perforation
3 animals dying under 5 months	4, 4, 4, 5	None	Intussusception, intra abdominal hernia meningitis
7 animals dying after 5 months	6, 6, 6, 5, 9, 11, 12	None	In 4, pneumonia after an exploratory operation or distemper,† in 2, intra abdominal hernia or adhesions in 1, abscess of the liver
4 animals	24	None	Etherized
2 animals	21	None	Etherized
1 animal	19	None	Etherized
1 animal	17	None	Etherized
1 animal	16	None	Etherized
1 animal	13, 5	None	Died after an exploratory operation intestinal obstruction

* Ulcer developed in only 3 of the 23 animals treated with aluminum phosphate gel.

† An exploratory operation was performed to prove the absence of ulcer. For example, such an operation was performed on dog 11 ten months after the initial operation. No ulcer was found. Treatment was withdrawn, and tarry stools appeared nine weeks later. Treatment was started, and the ulcer was pronounced clinically healed in four weeks. The dog died two weeks later from obstruction due to adhesions. The ulcer was healed.

five weeks (exploration) in the other dog. These results, along with those in 8 other dogs, are shown in table 5. Healing was demonstrated in all dogs by exploration or by autopsy. Spontaneous remissions of an ulcer in Mann-Williamson dogs have not been observed.

Gastric Analyses—An analysis of the gastric contents of the treated animals was made at 11 a. m. on a number of occasions. Free acid was uniformly found. Thus, gastric acidity was not completely controlled.

Nutrition—The general nutrition of the animals was always excellent, except when the therapy was withdrawn in the experiments on healing. All of the animals gained weight under therapy and while on treatment were heavier than they were before operation.

Anemia—After the animals had received aluminum phosphate gel for several months, anemia was observed (table 6), although there was

no evidence of the presence of ulcer. It was suspected that the anemia was due to iron deficiency, although there is no direct evidence showing that excessive phosphates in the diet actually interfere with the absorption of iron.⁷ One would not necessarily expect aluminum phos-

TABLE 5—Results of Aluminum Phosphate Gel Therapy on the Healing of Ulcer^x

Dog † No	No Therapy, Ulcer Developed, Weeks*	Therapy, Ulcer Healed, Weeks	No Therapy, Ulcer Developed, Weeks	Therapy, Ulcer Healed, Weeks	Comment
1	9	16	6	4	Killed at 20 months, scar found
2	14	11	7	5	Exploratory operation, no ulcer at 24 months
		(exploratory operation)			
3	16	12	Exploratory operation 1 month later, scar found		
4	11	10	Exploratory operation 1 month later, scar found		
5	6	8	Exploratory operation 6 weeks later, scar found		
6†	5	10	Exploratory operation, healed scar		
7	9	5	Exploratory operation at 1 month, healed scar found		
8	8	8	Exploratory operation 6 weeks later, scar found		
9	9	7	Exploratory operation 2 months later, scar found		
10	8	8	Died of obstruction at 13 5 months, ulcer healed except for an area 1 by 2 mm		

* The dogs did not have an ulcer nine to eleven and a half months after the beginning of the experiment, as shown by exploratory operation. The presence of ulcer was diagnosed by loss of weight and by the appearance of anorexia and tarry stools. The healing of ulcer was diagnosed clinically by the disappearance of tarry stools and anorexia and by the return to the original weight. It was diagnosed anatomically by exploration or by autopsy.

† The 20 and 24 months referred to in the case of dogs 1 and 2 means that the dogs were observed for that period and then autopsies were performed or they underwent exploratory operation and no ulcer was found. Dogs 3 to 9 are still alive at the end of a period of from 18 to 24 months.

‡ In this dog on withdrawal of therapy a second time an ulcer developed which refused to heal (exploration) completely. The dog refused to eat raw liver and pancreas, which was then fed by force. The ulcer healed in six weeks.

TABLE 6—Presence of Anemia and Response to Parenteral Iron Therapy in Mann-Williamson Dogs Receiving Aluminum Phosphate

	No of Dogs	Red Blood Cells	Hemoglobin, Gm /100 Cc	Hematocrit Reading
Normal for dogs before operation	30	Range 5,700,000 8,000,000 Average 6,900,000	Range 12 16 Average 14 5	Range 41 55 Average 47 5
Before iron therapy	12	Range 3,300,000 5,700,000 Average 4,700,000	Range 9 1 13 Average 11 0	Range 25 41 Average 35 0
One to 2 months after iron therapy	11	Range 4,800,000 7,200,000 Average 6,330,000	Range 10 2-14 3 Average 12 7	Range 34 46 Average 41 4
Final, 2 to 4 months on iron therapy	11	Range 5,470,000 8,000,000 Average 6,800,000	Range 11 3 16 0 Average 13 4	Range 35 48 Average 42 6

phate to interfere chemically with the absorption of iron, yet this should be determined by actual experiment.

Since we could not afford to lose time in the management of our animals, 35 mg of iron in the form of a dialyzed preparation of ferric

7 Brock, J. F., and Diamond, L. K. Rickets in Rats by Iron Feeding, *J. Pediatr.* 4:442, 1934. Day, H. G., and Stein, H. J. The Effect upon Hematopoiesis of Variations in the Dietary Levels of Calcium, Phosphorus, Iron and Vitamin D, *J. Nutrition* 16:525, 1938.

oxide (a 0.5 per cent solution⁸) was given intravenously each week. The hemoglobin content and red cell count returned to control levels (table 6).

It should be noted that the stools of the dogs given aluminum phosphate gel are firm, whereas the stools of untreated Mann-Williamson dogs are usually mushy.

Comment—We have used various therapeutic agents, such as alkalis, gastric mucin, various diets and aluminum hydroxide gel, on Mann-Williamson dogs. None has yielded such decisively favorable results as aluminum phosphate gel. Gastric mucin is definitely better than alkalis and aluminum hydroxide gel, as used by Oindorff, Fauley and Ivy,^{2d} but is inferior to aluminum phosphate gel. The adjunctive role played by the diet we use is illustrated by dog 6, table 5. An unfavorable observation is the fact that aluminum phosphate gel in the relatively large doses used with the animals apparently caused anemia, but this condition may tend to occur when aluminum therapy of any sort is used with Mann-Williamson dogs. This cannot be decided for aluminum hydroxide gel, since this preparation does not prevent ulcers from developing which per se cause anemia. This observation emphasizes the predictable fact that the administration of large doses of mineral salts which react with the acidic or alkaline juices, whether such salts are absorbed or not, interferes with the natural mineral metabolism of the body. However, this disadvantage appears to be reduced to a minimum by the use of a relatively inert substance, such as aluminum phosphate, which buffers acid and has a mildly astringent effect.

The results with aluminum phosphate gel were so favorable that we decided to administer it to patients with peptic ulcer to ascertain if it might be of value in their management.

USE OF ALUMINUM PHOSPHATE GEL IN TREATMENT OF PATIENTS

Duodenal and Gastric Ulcer—All except 6 of the patients were treated without rest in bed, 1 of these had a profuse hemorrhage, and the others had severe distress which failed to respond to other management.

An ulcer diet was prescribed during the active stage of the ulcer, but it was not carefully followed by one fifth of the patients (dispensary patients). During the active stage of the ulcer, a dose of 15 cc., or occasionally 30 cc., of aluminum phosphate gel every two hours was prescribed. Later in the course of management, a dose of 50 cc. with the meals and at bedtime, or 30 cc. six times daily with and between meals, was prescribed.

The type of ulcer treated and the results, except in the 3 cases of gastroduodenal ulcers, are shown in table 7. The diagnosis in all cases was supported by roentgen examinations.

The ulcer craters filled in (fig 2), with 1 exception. This was the case of a patient whose condition was diagnosed as "subacute perforation" of a duodenal ulcer. This patient was not relieved by any therapy and was subjected to operation. Another failure occurred in the case of a patient with duodenal ulcer who had had many recurrences. In this instance, night distress was not controlled. He responded to rest, mucin and aluminum phosphate gel. Another patient with duodenal

TABLE 7—*Results of Aluminum Phosphate Therapy in Human Patients*

Patients with duodenal ulcer total 32, bleeding 24, hemorrhage 2, crater 6	
Patients with gastric ulcer total 2, bleeding 2, hemorrhage 1, crater 2	
Dose of AlPO_4 : 15 cc every 2 hr (300 cc per day), or 50 cc with meals t i d and at bedtime	
Group I Patients with first attack	
A Response to AlPO_4	3
B No response to AlPO_4	0
*C Poor response to other management but active response to AlPO_4	2
D Failure to respond completely to any management	0
Group II Patients with numerous recurrences	
A Complete response to other managements and also to AlPO_4	13
*B Complete response to other managements during previous attacks but not during the present attack, complete response to AlPO_4	4
*C Response to a management during one or two attacks, no response to the same management, but active response to a different management during succeeding attacks, response to AlPO_4 during present attack	8
D Incomplete response to all managements, including AlPO_4	4

* These results are not to be given undue weight, since the severity of different attacks in the same patient varies. Lack of response to a management in two to five weeks followed by a prompt response to a change in management does not mean necessarily that the second management is better than the first, because continuation of the first management may have been successful if given more time and the psychotherapy of a change or "the new" may be involved.

ulcer had a hemorrhage after fourteen days under treatment with aluminum phosphate and an ambulatory regimen. He then responded promptly to management with rest, restricted diet, mucin and aluminum phosphate. Treatment of a fourth patient with duodenal ulcer was counted a failure because he complained of intermittent atypical distress during several months of therapy. The same distress occurred regardless of the type of management. Since the roentgen signs improved during management, hypochondria was suspected.

An accurate, statistical statement cannot be made regarding the time of relief from distress and the disappearance of blood because of the variability (twenty-four hours to three weeks) in this relatively small series of patients. The hemoglobin content of the blood and the erythrocyte count were followed in the majority of patients. A tendency

to anemia was not observed. A tendency to constipation (hard stools) was noted, and some type of liquid petrolatum was rather frequently administered.

Postoperative Gastrojejunal Ulcer—Three patients with marginal or jejunal ulcer were available for treatment. The condition of 1 patient, during a third recurrence, was diagnosed as "subacute perforation," with rigidity, an elevated temperature and a high leukocyte count. He did not respond to mucin and calcium carbonate therapy for one week, but responded promptly to aluminum phosphate therapy and became ambulatory in ten days. He continued to take aluminum phosphate for six months, after which he stopped treatment, and distress returned a year later. This recurrence responded promptly to aluminum phosphate therapy. The second patient, while on alkaline therapy, was hospitalized for a subtotal gastrectomy. Aluminum phosphate was substituted for

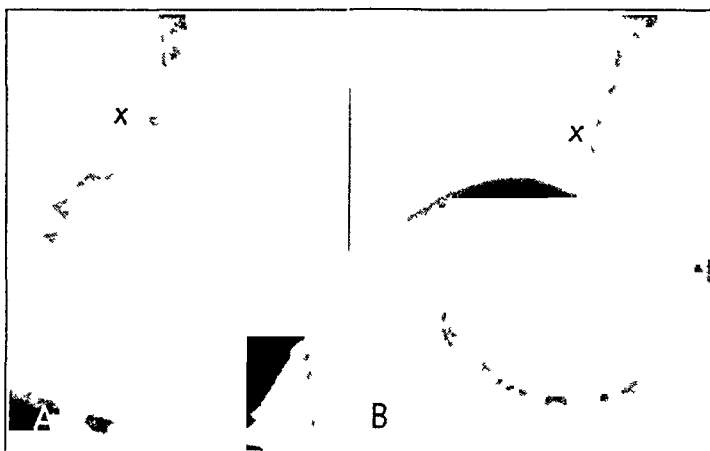


Fig 2—The response of a gastric ulcer to aluminum phosphate gel. *A*, gastric ulcer with crater. *B*, disappearance of crater. This picture was made eight weeks after institution of therapy with aluminum phosphate gel combined with a "soft" diet under ambulatory management.

the alkalis, and the patient was sent home after ten days without an operation, which still, six months later, with the patient under aluminum phosphate management, appears to be unnecessary. The third patient, during a third recurrence, responded promptly to aluminum phosphate gel. This patient had responded well to gastric mucin during the previous recurrences. We hope to study other patients of this type because of the similarity of their condition to that in our experimental animals.

Comment—With reference to table 7, the results in patients in group I C and group II B and C should not be interpreted as indicating that aluminum phosphate therapy is superior to other therapies. It must be kept in mind that the severity of attacks varies even in the same

patient. Lack of response to a management in from two to five weeks followed by a prompt response to a change in management does not necessarily mean that the second management is better than the first. The first management might have been successful if it had been continued longer. Also, the possibility of a psychic factor and of a spontaneous remission has to be considered, factors that are not encountered in our animal experiments. The results in the patients only indicate that aluminum phosphate gel has the promise of being as effective as any other similarly acting medicament in the management of peptic ulcer. This promise is supported, we believe, by the most decisive results of animal experimentation to be found in the literature. As stated before, our experimental results do not necessarily imply that aluminum phosphate gel is superior to aluminum hydroxide gel for the management of peptic ulcer in man except in the presence of a relative or an absolute deficiency of pancreatic juice and bile.

COMMENT

We were particularly interested in testing aluminum hydroxide gel on Mann-Williamson dogs because it was found by Orndorff and his associates^{2d} and by McCann^{2f} that such dogs usually manifest a continuous secretion of gastric juice, which apparently cannot be controlled by atropine. This observation suggested (Orndorff and his associates^{2d}, Ivy and Bachrach^{8a}) that the hypersecretion might be due to the elaboration of histamine by the irritated jejunal mucosa in amounts too large to be inactivated by the histaminase in the irritated mucosa. It was thought that an astringent and demulcent, such as aluminum hydroxide, might reduce the irritation and reduce the hypersecretion.⁴ In addition, it would serve as an antacid. We believe, as has been suggested by Einsel, Adams and Myers and associates⁹ that the astringent and the demulcent properties of aluminum hydroxide or aluminum phosphate, as well as their antacid property, are of therapeutic value. It is also possible that they increase the secretion of mucus. But how they actually operate to produce a favorable effect is still an open question.¹⁰

8a Ivy, A. C., and Bachrach, W. H. An Abnormal Mechanism for the Excitation of Gastric Secretion in the Dog, *Am J Digest Dis* **7** 76, 1940.

9 Einsel, I. H., Adams, W. L., and Myers, V. C. Aluminum Hydroxide in the Treatment of Peptic Ulcer, *Am J Digest Dis* **1** 513, 1934. Adams, W. L., Einsel, I. H., and Myers, V. C. Aluminum Hydroxide as an Antacid in Peptic Ulcer, *ibid* **3**:112, 1936. Quigley, J. P., Einsel, I. H., and Meschan, I. Some Effects Produced in the Normal Stomach by the Ingestion of Moderate and Massive Quantities of Aluminum Hydroxide Gel, *J Lab & Clin Med* **24** 485, 1939.

10 Komarov, S. A., and Krueger, L. The Effect of Aluminum Hydroxide Gel on Gastric Secretion in the Dog, *Am J Digest Dis* **7**:170, 1940. Footnote 9.

SUMMARY

It was shown previously that aluminum hydroxide gel has no value in preventing postoperative jejunal ulcer in Mann-Williamson dogs in the presence of a relative deficiency of pancreatic juice and bile. This lack of benefit was ascribed to the production of a phosphorus deficiency. Data presented in this paper show that aluminum hydroxide gel in relatively large doses interferes with the absorption of phosphates in man and dog. It may produce a phosphorus deficiency in the presence of a relative deficiency of pancreatic juice, diarrhea or a low phosphorus diet. It should not produce a phosphorus deficiency in the usual patient with ulcer on the ordinary ulcer diet, which is relatively rich in phosphorus.

Aluminum phosphate gel has antacid, astringent and demulcent properties analogous to those of aluminum hydroxide gel and does not interfere with phosphate absorption. It was used, therefore, to give aluminum gel therapy a fair experimental trial under rigidly controlled conditions and under the most severe test known experimentally, namely, the healing of jejunal ulcer in Mann-Williamson dogs. Aluminum phosphate gel administered with a special diet prevented the development of ulcer in all but 3 of 23 Mann-Williamson dogs. After an ulcer developed, as a result of the discontinuance of aluminum phosphate gel, the administration of the gel caused complete healing of the ulcer in 9 of 10 dogs. This is a striking result. The results of the use of aluminum phosphate gel on a small series of patients with peptic ulcer indicate that the preparation has promise of being as effective as any other similarly acting medicament in the management of peptic ulcer. Our experimental results do not necessarily imply that aluminum phosphate gel is superior to aluminum hydroxide gel for the management of peptic ulcer in man except in the presence of a relative or an absolute deficiency of pancreatic juice, diarrhea or a low phosphorus diet.

ABSTRACT OF DISCUSSION

DR JESSE L. BOLLMAN, Rochester, Minn. When Dr Ivy gives a paper he leaves little to be discussed. I should like to emphasize the value of the extensive controls for the Mann-Williamson dog, of which Dr Ivy and associates have spoken. In my experience, students in starting out to perform the Mann-Williamson operation are almost universally unsuccessful in obtaining ulcers. After more experience has been gained, ulcers develop in all the dogs and most of the forms of therapy which at first seemed successful result in failures. I should say that the controls that Dr Ivy and his co-workers have used—the development of ulcer in the dog after operation, the curing of the ulcer with the therapy described and the cessation of therapy followed by the redevelopment of ulcer—can be taken as absolute controls. This is the first method by which absolute cure of an ulcer produced in a Mann-Williamson dog has been demonstrated. I should like to ask Dr Ivy a question. In giving substances such as aluminum hydroxide and

aluminum phosphate, which he has shown take from the intestine various inorganic elements, is it not possible that there are a large number of other substances absorbed? Perhaps in these experiments the amount would not be sufficient to be serious, but in continued therapy with highly absorptive colloids I believe that one is going to get into trouble with undesired absorptions. I have particularly in mind the absorption of vitamin B. It could well be absorbed by either the aluminum hydroxide or the aluminum phosphate.

DR. HYMAN I. GOLDSTEIN, Camden, N. J. In all the experiments as carried out on dogs by Dr. Ivy and associates, the element of mental worry and anxiety and the resulting effects on the autonomic vegetative nervous system is entirely absent. One is now not so sure that the factor of hyperacidity is the all-important one from the standpoint of the cause of peptic ulcer. All know that the "go-getter," the hard working fellow, the man who has lost money, the man who is always "on the go," the thinker is the person in whom ulcer of the stomach or duodenum develops.

In recent years one sees a far greater number of duodenal ulcers than gastric ulcers, although the duodenal ulcer develops in an essentially alkaline medium. All have seen many cases in which ulcers healed in patients with marked hyperacidity. Peptic ulcers do not often develop in patients with continued hyperacidity. Some years ago there was considerable interest in attempts to try out other antacid and adsorbent remedies, beginning with the work of Greenwald (1923), Kantor (1923), Mutch (1936, 1937), Mann (1937), Tidmarsh and Baxter (1938), Kramer (1938), Winkelstein, Woldman and Rowland, H. I. Goldstein (1937) and others. Five or six years ago I began to replace the so-called Sippy form of therapy with other measures, including the use of aluminum hydroxide, kaolin (aluminum silicate) and, more recently, magnesium trisilicate. Joannes Scultetus used kaolin about three hundred years ago in the treatment of similar gastrointestinal disturbances, while Aurelius Cornelius Celsus, nearly two thousand years ago, treated ulcers of the stomach and advised an antacid diet¹. I might mention, too, the old report by Sommer (1696) on "De ardore ventriculi" and his use of soda for hyperacidity, the discussion by Rivinus (1677) entitled "De acido ventriculi fermento," the use by Richter (1794) of "alkaline and absorbent medicines" and a "dieta antacida" and, finally, the employment by Trousseau and Bonnet (1832) of sodium bicarbonate in "painful stomach." The story of ulcer of the stomach and duodenum is an old one, and one must not feel disappointed at one's failure to have at this late date complete and accurate knowledge of the cause of ulcer and its certain cure.

I should like to ask Dr. Ivy whether there is any particular advantage in using aluminum phosphate in place of aluminum hydroxide in clinical practice or such a combination as I have employed during the past three or four years of magnesium trisilicate (50 per cent), kaolin (25 per cent) and aluminum hydroxide (25 per cent) in helping to avoid the chemical changes which he has discussed.

While my own experience has been entirely clinical, and not with Mann-Williamson dogs, the results in my cases have been better after the use of the aforementioned remedies than with the old form of alkaline therapy.

DR. I. H. EINSEL, Cleveland. I have used aluminum hydroxide gel for twelve years. In a large series of cases I have not seen any deleterious effects, except in 2 instances. Both were cases of gastrojejunal fistula in which the patients were in an emaciated state due partially to the diarrhea with resulting avitaminosis. They were placed under treatment with the usual dose of aluminum hydroxide gel for several weeks. Instead of improving as one would expect, they became

worse This necessitated their removal from the aluminum hydroxide therapy After small feedings of the usual ulcer diet with high vitamin intake they improved

At the time I could not explain the failure of these patients to respond to the aluminum hydroxide gel therapy, but it can readily be explained by Dr Ivy's observation that aluminum hydroxide gel causes a disturbance in the phosphorus metabolism under certain physiologic conditions

In the beginning of aluminum hydroxide therapy there is a slight loss of appetite I have noticed this many times Apparently after ten days this loss of appetite disappears, and the patient continues his therapy with no difficulty This may be caused by the disturbance of phosphorus metabolism by the aluminum hydroxide The paper by Dr Ivy and his associates has been of great interest to me

Dr A C Ivy, Chicago With regard to the effect of aluminum gels on absorption, there is one point that I neglected to mention In our animals receiving relatively large doses of aluminum phosphate gel there appeared iron deficiency anemia, or anemia that we interpreted as iron deficiency anemia on the basis of therapeutic results We injected colloidal iron intravenously, 35 mg per week, and the anemia was controlled

We cannot state absolutely that aluminum phosphate interferes with the absorption of iron, but there are reasons why large quantities of any phosphate may do so As a matter of fact, when minerals which react with the acid and the alkaline juices are introduced in large quantities into the alimentary tract, one can expect in the course of time to produce some change in mineral metabolism

It is possible for aluminum phosphate or aluminum hydroxide to interfere with the absorption of vitamins Our animals, however, received 200 Gm of raw ground pancreas and 200 Gm of raw ground liver daily, so they were adequately supplied with vitamins If the vitamin content of the diet is low, then these gels may interfere significantly with the absorption of vitamins I know how important the anxiety factor is in the production of peptic ulcer in human beings I believe that the most direct attack on the etiologic agent of peptic ulcer in man, in the majority of cases, is to teach the patient how to eat and how to live, he must learn to relax and to forget his worries This is frequently difficult The ulcer that we obtain in the Mann-Williamson dog, in my opinion, is analogous to the ulcer that occurs postoperatively in man, after gastrojejunostomy, and our results should be most applicable to cases of that type Magnesium trisilicate is a better and a cheaper "antacid" than aluminum phosphate gel, but I suspect that in our experimental animals we shall not obtain as good results with magnesium trisilicate because it does not possess a mildly astringent property We plan to test the trisilicate on the experimental animal

ACUTE SCLEROSING VASCULAR DISEASE WITH RENAL CHANGES

REPORT OF A CASE

ROLF KATZENSTEIN, M D

AND

JAMES PETER MURPHY, M D

NEW HAVEN, CONN

The clinicopathologic entity of bilateral cortical necrosis of the kidneys has been well recognized, especially since the comprehensive summary, which included 2 of the author's own cases, published by Ash¹ in 1933. Many articles presenting more examples of this strange condition have appeared since then.² In all the clinical course was characterized by one or more of the following features: absence of premonitory signs or symptoms of renal damage, acute onset of the illness (frequently subsequent to the termination of pregnancy), reduction or suppression of urinary output, elevation of systolic and diastolic blood pressures (in about one half of the cases), headache, unconsciousness and convulsions (the last occurring in about one third of the cases), vomiting and diarrhea, and a short course, terminating fatally in one to nineteen days. Coma usually preceded death. Albuminuria and the presence of erythrocytes and casts in specimens of urine examined were almost constant observations, nitrogen retention was variable.

At necropsy the macroscopic appearance of the kidneys was striking. The whole or part of the cortical tissue of both organs was swollen, opaque, putty colored and well demarcated from the normal medulla by

From the Department of Pathology, Yale University School of Medicine

The clinical data are included with the permission of the Department of Internal Medicine, Yale University School of Medicine

1 Ash, J. E. Bilateral Cortical Necrosis of the Kidneys (Angioneurotic Anuria), *Am J M Sc* **185** 71, 1933

2 Bowes, R. K. Renal Cortical Necrosis Associated with Pregnancy, *Proc Roy Soc Med* **27** 1505, 1934. De Navasquez, S. Histology and Pathogenesis of Bilateral Cortical Necrosis of Kidney in Pregnancy, *J Path & Bact* **41** 385, 1935. Evans, N., and Gilbert, E. W. Symmetrical Cortical Necrosis of Kidneys, *Am J Path* **12** 553, 1936. Gaspar, I. A. Bilateral Cortical Necrosis of Kidneys, *Am J Clin Path* **8** 281, 1938. Garvin, C. F., and Van Wezel, N. Bilateral Cortical Necrosis of Kidneys. Report of Case, *Arch Int Med* **62** 423 (Sept.) 1938. Weaver, R. G., and von Haam, E. Cortical Necrosis of Kidney Following Tonsillitis, *ibid* **63** 1084 (June) 1939.

an intervening zone of congestion. Microscopically, this cortical necrosis was found to replace areas corresponding to the distribution of the interlobular arteries. These vessels, as well as their branches, had necrotic walls and were occluded by thrombi of any variety. Epithelial cells of the tubules and, to a varying degree, glomeruli were destroyed. The arcuate arteries were spared.

The onset and progress of the disease in the case herein reported closely conform to the clinical picture just described. The pathologic findings, however, were unusual and were not in accord with the diagnosis of bilateral renal cortical necrosis.

REPORT OF CASE³

G. S., an unmarried woman of 22, was admitted to the New Haven Hospital on Dec. 22, 1939, in a state of coma which followed several convulsive seizures.

Family History—None was obtained.

Past History—In September 1938 an appendectomy was performed for "chronic, recurrent appendicitis." The patient complained of "stiffness" of the hand and fingers in June 1939. This "arthritis" persisted for seven weeks, during which time three teeth were extracted, after the extraction the "arthritis" subsided completely. The patient was admitted to another hospital in September 1939, three weeks before the terminal illness, because of abdominal distress diagnosed as "visceroptosis" and "pylorospasm." The results of urinalysis and the recordings of the blood pressure at that time were within normal limits.

Present Illness—Three weeks before her last admission to the hospital the patient began to experience severe frontal headaches, accompanied by nausea. One week later nocturia appeared and became persistent. Shortly (exact time unknown) prior to entrance into this hospital she is said to have had a "sore throat" and "sinus trouble." The night immediately preceding admission she complained of dizziness and not long thereafter underwent a series of generalized convulsions, which were followed in turn by unconsciousness. In this state she was brought to the hospital.

Physical Examination—The temperature was 97° F. (rectal), the pulse rate 100 to 120 per minute, the respiratory rate 20 per minute and the blood pressure 210 mm. of mercury systolic and 120 mm. diastolic.

The patient was comatose and restless. The pupils were equal and responded to light and in accommodation. Each optic nerve head was "blurred", the fundic veins were tortuous, but no hemorrhages were seen. The heart was overactive but not enlarged, a systolic murmur was heard over the whole precordium. On percussion and auscultation both sides of the chest were clear. Examination of the abdomen revealed nothing abnormal. There were no definite paralyses. The left radial and left patellar reflexes were absent. Positive Babinski and Hoffmann responses were not obtained.

The results of urinalyses made at the time of admission and afterward and the values for the chemical constituents of the blood are recorded in the table.

Course—Shortly after admission the patient was given paraldehyde rectally and a hypertonic solution of magnesium sulfate intravenously. Cultures of material

³ The abstract of the history in this case was taken from the files of the department of internal medicine.

from the throat disclosed the presence of a beta hemolytic streptococcus, of an unknown group. Two days later the patient was comfortable, but the blood pressure (190 systolic and 112 diastolic) had not dropped appreciably. The next day the first of several convulsive episodes occurred, these were characterized by generalized clonic and tonic movements, without incontinence or pathologic reflexes. They were followed by unconsciousness for variable periods. One week after admission there was a short period of coma uncomplicated by epileptiform activity. Recovery from this last episode was rapid, but headache (which had reappeared) persisted. Three days later inspection of the eyegrounds revealed bilateral retinal detachments and a hemorrhage in the left fundus. The next day the patient again had a convulsion, and the temperature was slightly elevated (101 F). By January 11 the patient had lapsed into a deep stupor, in which she remained until death. During this time there were continuous "twitchings" of the eyelids and the left thumb, rotary movements of the right hand and dorsal clonic flexion of the left foot, severe epileptiform seizures occurred immediately before death. She died on Jan 12, 1940, the fifteenth day of hospitalization. The blood pressure had remained constantly around 210 systolic and 120 diastolic. The output of



Fig 1—Surface of the kidney. Depressed areas in the cortex, corresponding to the distribution of occluded vessels, alternate with zones of elevated, normal tissue.

urine was slightly reduced during the early days of the illness, but was approximately two thirds of the fluid intake during the final week.

Observations at Necropsy—Examination of the body was performed three and one-half hours after death. The skin and the mucous membranes were pale. A well healed scar was observed in the right lower quadrant of the abdomen. Subcutaneous hematomas were noted around marks of needle punctures in either antecubital space and on the anteromedial surface of the left thigh. Both pupils were round, the diameter of the right one was 6 mm and that of the left 4 mm. The vulval region was edematous. Two hundred cubic centimeters of clear amber fluid was contained within the smooth serosal lining of the abdominal cavity, fibrous adhesions bound the cecum to the internal surface of the abdominal parietes. Each pleural space contained 200 cc of clear yellow fluid and was lined by a glistening surface. Ten cubic centimeters of turbid yellow fluid was found within the intact pericardial envelope. The remnant of the thymus was small.

The right kidney weighed 150 Gm and the left 140 Gm, they were almost exactly alike. The fibrous capsules of these organs were thin and could be stripped from the cortical surfaces with ease. Many irregularly shaped depressions, discoid or roughly rectilinear and dark red, occurred on the surfaces of the

kidneys These areas alternated with ones of smooth, gray-red, well preserved tissue The shape and arrangement of the depressions were reminiscent of the scars so frequently seen in the senile kidney (fig 1)

Laboratory Data

Date	Reaction	Urinalyses *					Blood Chemistry					
		Specific Gravity	Albumin	Casts	Red Blood Cells	White Blood Cells	Nonprotein Nitrogen, Mg per 100 Cc	Serum CO ₂ , Volume per Cent	Serum Cl, mEq	Total Protein, Gm per 100 Cc	Albumin, Gm per 100 Cc	Dextrose Gm per 100 Cc
12/29/39		Q N S	4+	Several	Occasional	0	40	60.3	87.9	8.27	3.8	4.44
12/30/39	Acid	1.022	4+	2-3 granular casts	2-3	Rare	50	60.6	85.5			
12/31/39	Acid	1.005	3+	0	0	Rare						
1/2/40	Alkaline	1.007	3+	Occasional granular cast	Rare	0	29	84.2	81.2	6.75	3.32	3.43
1/5/40	Alkaline	1.008	3+	0	6	1	24	82.1	79.9			
1/8/40	Alkaline	1.008	2+	0	Occasional	Occasional	34	70.2	75.0	5.59	2.94	2.65
1/10/40	Alkaline	1.005	3+	0	Occasional	Occasional						
1/15/40							24	74.3	72.2			

* Tests for sugar and acetone in the urine consistently gave negative results, a sample of blood taken on Jan 8, 1940, contained 8.52 mg of calcium and 3.11 mg of phosphorus per hundred cubic centimeters

Blood Counts

Date	Red Blood Cells	Hemoglobin	White Blood Cells	Poly-morpho-nuclears	Neutrophils, Nonsegmented Forms	Lymphocytes	Large Mono-nuclears	Eosinophils	Basophils	Smear
12/29/39	5,440,000	16.5 Gm	39,400	95	15	6	0	0	0	7 myelocytes per 100 white blood cells
1/8/40	4,120,000	14.0 Gm	25,700	91	19	7	1	1	0	5 myelocytes per 100 white blood cells
12/29/39	Kahn reaction of blood negative									
1/8/40	Excretion of phenolsulfonphthalein first hour, 5%, second hour, 13%, third hour, 10%, total, 28% Electrocardiographic report 3-2 arterioventricular block, abnormal T waves, abnormal duration of Q-T interval									
1/11/40	Cerebrospinal fluid diffusely bloody, red blood cells, 10,500 per cu mm, total proteins 81 mg per 100 cc, Kahn reaction negative									

When the kidney was sectioned the parenchyma did not bulge from the capsule The width of the cortex in the areas corresponding to the depressions observed externally was much reduced The tissue here was deep red, and the striations were distinct Streaks of the same color extended into the superficial portions of the pyramids The width of the cortex in between these zones was normal, the striations were blurred, and the glomeruli were just visible No gross hemor-

rhages were seen anywhere, and no opaque areas suggestive of necrosis could be discovered. The medullary pyramids were of the same color as the narrow zones in the cortex, and their rays were accentuated by vascular engorgement.

The main renal arteries, although their lumens were small, had thin, translucent walls and an intact intima free of plaques. The interlobar arteries which led to the areas of cortical depression had thick walls, and gray, mucoid material almost completely occluded their channels. The main renal veins were not thrombosed, and their inner linings were smooth.

The walls of the pelvis and calices were not increased in thickness and were lined by pale, intact mucosa. The mucosal surfaces of the ureters and the bladder were also well preserved. The muscularis of the latter organ was not increased in width.

The heart weighed 250 Gm. Subendocardial petechiae marred the inner surface of the left ventricle. The smallest visible branches of the coronary arteries were similar to the arteries of the kidney, the walls were gray and thick, and the lumens were absent. Each lung weighed 350 Gm., the lower lobes were edematous and congested. Small deposits of yellow material (atheroma), resembling candle drippings in contour, were seen on the internal surface of the aorta, especially near the ostiums of vascular branches.

The tissue of the brain was pale and slightly edematous, the leptomeninges were thin and perfectly translucent. There was but little flattening of the convolutions, however, the cerebellar tonsils had herniated through the foramen magnum to a slight degree. All the major pial vessels had thin, elastic walls and unoccluded lumens.

When sectioned in a frontal plane, the cerebral hemispheres were found to be sprinkled with many petechial hemorrhages, most of which lay in the cortical gray matter. The left frontal lobe was especially affected, but there were several petechiae in the striate bodies and some in the thalami. It also appeared that both the central and the cortical gray matter was involved in another fashion, perhaps by ischemia, for the coloration was not homogeneous, but somewhat mottled in a manner suggesting necrobiosis. The pons, the medulla and the cerebellum appeared not to be involved. There was no dilatation of the ventricular system.

Microscopic Observations—The tissues, except for the brain, were fixed in Helly's modification of Zenker's solution or in a 10 per cent concentration of solution of formaldehyde U S P, sectioned at 8 microns and stained with hematoxylin and eosin, with Masson's trichrome stain and with Weigert's stain for elastic tissue. The brain was fixed in a 10 per cent concentration of solution of formaldehyde U S P for one week, and after the tissue was properly embedded in pyroxylin, representative blocks were sectioned at 20 microns and stained by the Nissl technic.

Small Arteries The small arteries in the myocardium, spleen, liver, perirenal adipose tissue, kidneys, mesentery, intestinal submucosa and wall of the urinary bladder had a uniform appearance. (Under this heading are included arteries corresponding in size to the renal interlobar vessels, to those equal in magnitude to preafferent arterioles.) The lumens were extremely reduced, this reduction was due to the presence of a subendothelial tissue consisting chiefly of spindle-shaped fibroblasts and fibrocytes, among which were also seen small, round cells. Intercellular edema was present to some degree. Narrowing of the vascular lumens varied from constriction by an inward, button-like protrusion of the

intima to complete obliteration (fig 2) Portions or the whole of the muscular coat was replaced by this fibroblastic proliferation or by dense, hyalinized scar tissue The internal elastic lamina of the vessel wall was stretched, fragmented or completely absent, rarely, however, it was intact (fig 3) The adventitia was thickened by granulation tissue or by hyaline fibrous tissue Transverse section of some especially small vessels disclosed complete destruction of the vascular wall and lumen by granulomatous material



Fig 2—Tangential cut through an interlobar artery Connective tissue thickens the intima and replaces the media, granulation tissue is seen in the adventitia Masson stain, $\times 50$

Serial sectioning revealed progress in the severity of the damage in the same vessel Subendothelial thickening visible at one level gave way more distally to fibrosis of the media and changes in the adventitia

Kidneys Vascular changes were most striking in the kidneys, of all the organs examined The zones which appeared (macroscopically) dark red and depressed

proved on histologic examination to exhibit hyperemia of the glomerular capillaries and extreme narrowing of the lumens of the tubules. Rarely, adhesions and organization were seen in a tuft, but there was no necrosis, hyalinization or exudation in the capsular spaces. Numerous mitoses were seen in the tubules in the epithelial cells, which had well stained nuclei and intact cytoplasm. There was also moderate increase in interstitial connective tissue, and small vessels distended with erythrocytes were found here.



Fig 3—Interlobar artery. The elastic lamella is stretched and fragmented. Weigert stain, $\times 100$.

The areas of the cortex which, in gross appearance, were pale and not depressed, contained tubules with fairly wide lumens. The latter were partially filled with pink-staining, granular material. The tubular epithelium, in general, was high, and the cells had abundant, homogeneous, well preserved cytoplasm and well formed, round nuclei. The glomeruli in these regions disclosed a slight increase in the number of endothelial cells, the capsular epithelium was frequently seen to be swollen, and in a few capsular spaces there was a small amount of light pink, granular debris. Occasionally, the wall of a glomerular capillary

showed "fibrinoid" necrosis, as did those of a few afferent arterioles (fig 4). However, the necrotic changes in the afferent vessels and the glomerular capillaries were minimal in comparison with the arterial damage. Nowhere in the cortex of the kidney was actual necrosis seen.

Between the tubules of the pyramids there was present a small amount of "fibrinoid" material, which may or may not have been intravascular. The epithelium of the pelvis was several layered, and its individual cells were well preserved. There was a small amount of infiltration of round cells in the submucosa, the round cells were also found in the adventitia of the small vessels of the pelvis.

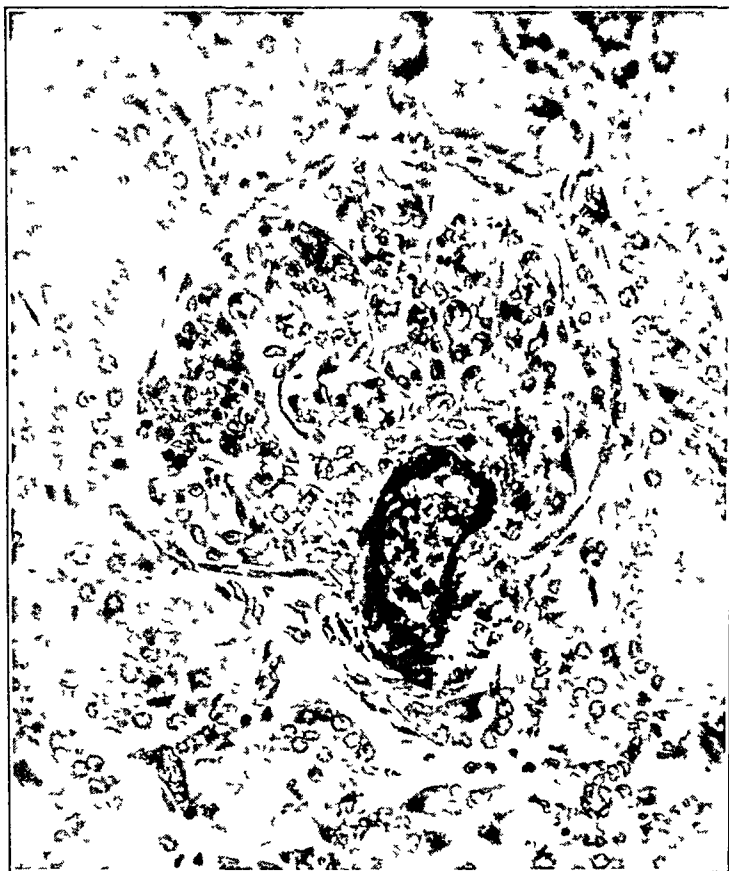


Fig 4—Glomerulus under high magnification. The afferent arteriole is necrotic and is dilated in a "lakelike" fashion. Hematoxylin and eosin, $\times 200$.

Brain. Here the histologic lesions were all referable to the small units of the vascular system and were most striking in the cerebral hemispheres.

Scattered erythrocytes as well as golden granular pigment lay in the edematous leptomeningeal spaces. Here and there, vessels of the arteriolar variety exhibited extreme swelling and proliferation of the endothelium, the nuclei of the cells of the intima being large, oval and lightly stippled, and rarely exhibiting mitoses (fig 5).

Surrounding many of the cortical and subcortical capillaries, arterioles and venules, pink, colloid-like material was seen in the Virchow-Robin spaces, indenting

the vascular walls Here again, especially in the cortex, swelling and proliferation of the endothelium were noted Occasionally, a round area of fresh hemorrhage was present in the gray matter (fig 6) Ganglion cells nearby were seen to be undergoing "severe" cell change, being shrunken and dark Astrocytes were swollen (as were the oligodendrocytes), had proliferated and were occasionally binucleate

Tiny focal areas of neuronal necrobiosis were also found in the cortex, chiefly in the superficial (first to third) laminae, here neurons were replaced by clumps of astrocytes, as well as microglial cells which had assumed the form of *Stabchencellen*

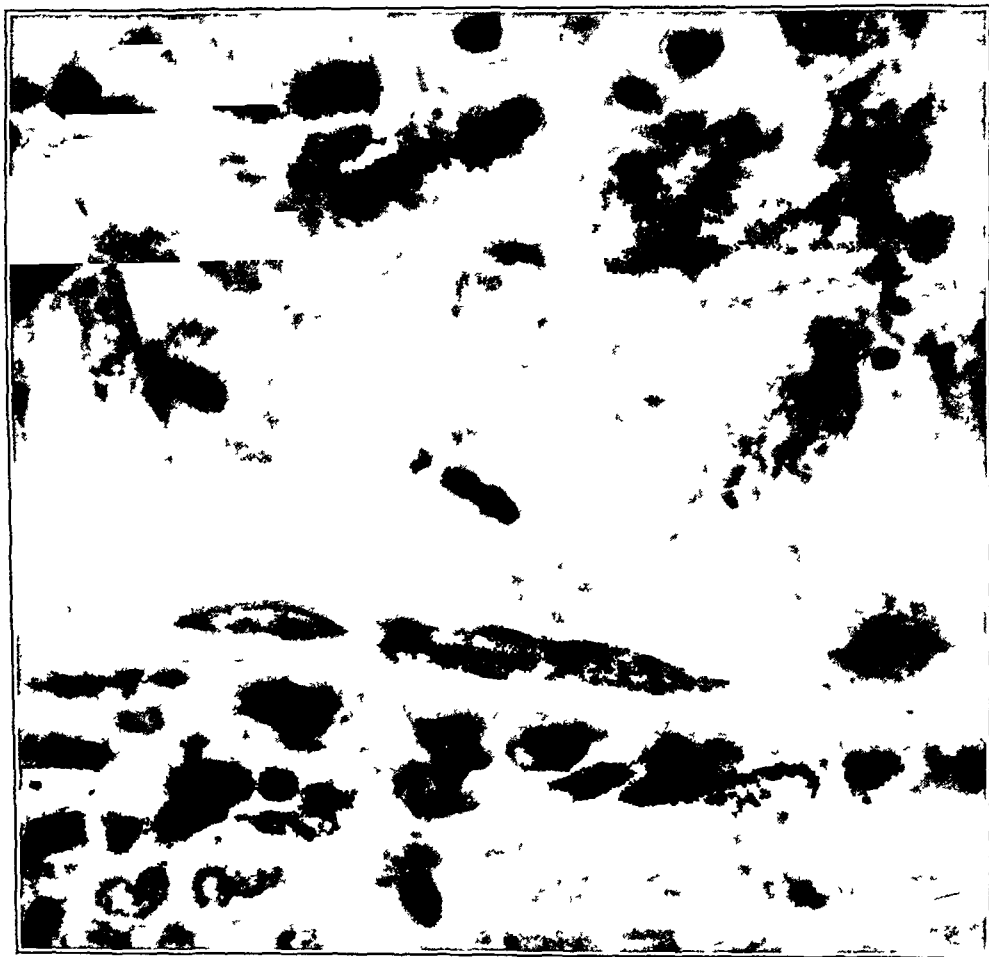


Fig 5—Proliferation of endothelial cells lining a pial arteriole A mitotic spindle is present in the center of the field Nissl stain, $\times 700$

Large mononuclear cells, filled with a green pigment containing iron, clustered in the adventitial and in the perivascular spaces of the vessels in the white matter Here, as well, glia cells were massed to form minute nodules, rarely around tiny capillary channels Several "stars" of Hortega cells and astrocytes lay in the medullary pyramids

One of the acoustic nerves was infiltrated with small, round cells A group of ganglion cells in the cerebellar roof nuclei were shrunken and dark, but there was no accompanying glial response

Other Organs The interstitial tissue of the heart was slightly increased and somewhat edematous There was no necrosis and no scarring of the myocardium

In the wall of a single pulmonary vessel, of small size, there was infiltration of polymorphonuclear leukocytes. Several arterioles in the pancreas had smudged, light pink (with Masson stain), necrotic walls. There was also some interstitial fibrosis. The muscularis of the urinary bladder was diffusely scarred in the vicinity of the damaged vessels. The malpighian corpuscles of the spleen consisted chiefly of "germinal center cells." Aside from the vascular change previously described, no significant histologic alterations were discovered in the liver, adrenal glands or small intestine.

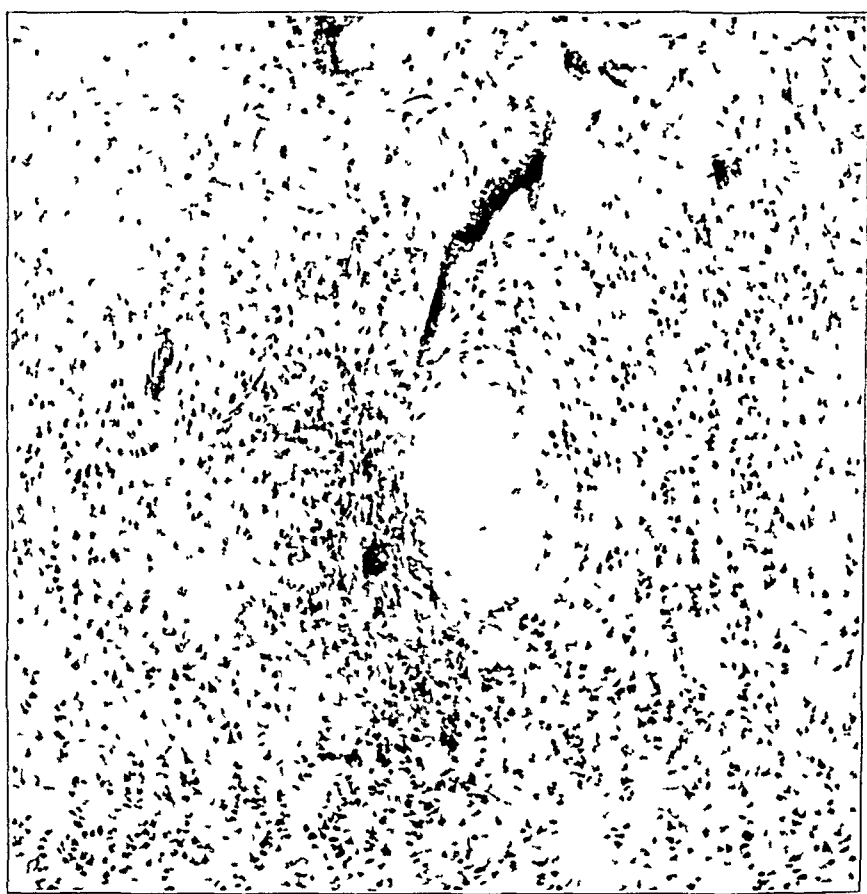


Fig 6—Round area of hemorrhage in the cerebral cortex. Shrunken ganglion cells and proliferated glia bound the extravasation. Nissl stain, $\times 60$.

COMMENT

The principal and, we believe, unique pathologic features in the case presented are (1) virtually exclusive involvement of small arteries (most striking in the interlobar vessels of the kidneys), (2) almost complete occlusion of the lumens of these arteries by subendothelial proliferation of young connective tissue cells, (3) absence of thrombi, (4) replacement of smooth muscle cells in the media by fibroblasts and fibrocytes, and (5) adventitial granulation.

It is difficult to decide on the proper classification of this process, and there is no suggestion, even remote, as to the cause. As emphasized by Buerger,⁴ thromboangitis obliterans is characterized by thrombosis of vascular channels, vascularization of the medial coat and a definite inflammatory reaction in the adventitial tissues, as well as by other features also absent in this case. Periarteritis nodosa (Klotz⁵) is recognizable by the presence of an acute inflammatory cellular infiltration in necrotic vessel walls, which are frequently the site of aneurysmal formations. None of the vessels described here were thus affected. Despite the previously mentioned similarity between the macroscopic renal lesions and those commonly seen in the kidneys of elderly people, the injured arteries failed to exhibit reduplication of the internal elastic lamellae or subendothelial atheromatous deposition and the glomeruli in the infarcted zones were not concentrically hyalinized.

The occasional arteriolar necrosis (kidney and pancreas) is of interest in the light of experimental production of these lesions (Goldblatt⁶) by renal ischemia. Small intracerebral hemorrhages, vascular changes, damage to ganglion cells and glial reaction, all strikingly similar to those observed in this patient, have been observed in the brains of nephrectomized dogs which have been given injections of extracts of kidneys.⁷

SUMMARY

An unusual case of vascular disease, occurring in a 22 year old woman, is presented. Sclerosing changes in small arteries, without thrombosis, characterized the vascular lesions. The cause of the condition is entirely unknown. Clinically, the illness simulated bilateral renal cortical necrosis. Arteriolar lesions (with subsequent cerebral injury) were noted, and their possible pathogenesis is commented on

4 Buerger, L. Thromboangitis Obliterans, *Am J M Sc* **136** 567, 1908

5 Klotz, O. Periarteritis Nodosa, *J M Research* **37** 1, 1917

6 Goldblatt, H. Experimental Hypertension Induced by Renal Ischemia Harvey Lecture, *Bull New York Acad Med* **14** 523, 1938

7 Winternitz, M. C., and others. Unpublished data

ESTIMATION OF THE ASCORBIC ACID (VITAMIN C) REQUIREMENT OF AMBULATORY PATIENTS

GRACE A GOLDSMITH, M D

ADOLPH T OGAARD, M D

AND

DONALD F GOWE, M D *

NEW ORLEANS

The daily requirement of the normal person for ascorbic acid is difficult to determine accurately, and the minimal and optimal quantities needed remain a subject of some controversy at the present time. It is generally accepted, however, that the deficiency of vitamin C which is of so frequent occurrence in infections and in conditions associated with heightened metabolism is due to an increased need for ascorbic acid by the body and not merely to a deficient supply in the diet. It seemed to us that it should be possible to compare grossly the requirements in health and in disease without detailed metabolic experiments. The object of this study was to evolve a method by which the ascorbic acid requirements of ambulatory patients attending an outpatient clinic could be estimated. Our interest in the problem was stimulated by finding a vitamin C deficiency to be extremely frequent in persons with bronchial asthma, even when their diets appeared to be adequate. In this paper are reported the results of studies on a number of essentially normal patients, who have been designated a control group. In a subsequent paper the findings in cases of bronchial asthma and other allergic conditions will be presented.

METHODS

The method devised for the study of vitamin C requirements consisted of placing the subject on a diet low in the vitamin, saturating his body tissues by giving him large doses of ascorbic acid¹ and then administering daily an amount of this substance which was believed sufficient to maintain saturation. The diet prescribed was not devoid of vitamin C, since enough variety was necessary to insure observance for several months. Foods containing a large percentage of ascorbic acid were omitted (table 1, list 1), while only one food containing moderate quantities of ascorbic acid was allowed daily (table 1, list 2). The values for the ascorbic acid content of foods were obtained from the tables published by Bessey²

* Formerly of New Orleans, now of St. Luke's Hospital, Ponce, Puerto Rico.

From the Department of Medicine, Tulane University of Louisiana School of Medicine, and the Charity Hospital of Louisiana.

1 Supplied by Merck & Co., Inc.

2 Bessey, O. Vitamin C. Methods of Assay and Dietary Sources, J. A. M. A. **111** 1290 (Oct. 1) 1938.

In order to start with comparable tissue stores of ascorbic acid, it was necessary to saturate each patient with this substance before placing him on a maintenance dose of ascorbic acid. Saturation was accomplished by the administration of 100 mg of crystalline ascorbic acid three times daily for one week and 100 mg twice daily for a second week. The continuance of a generous supplement of ascorbic acid for a second week allowed comparison of the level of this substance in the blood on two occasions and insured tissue saturation. Furthermore, if a marked deficiency existed at the onset of the experiment, this would be manifested by a retarded elevation of the ascorbic acid in the blood. After saturation was completed, the patient was given 50 mg of ascorbic acid daily. This amount was chosen somewhat arbitrarily. The daily requirement to prevent scurvy has been estimated at 25 to 30 mg,³ and that to maintain saturation, at 70 to 100 mg.⁴ We wished to

TABLE 1—*Diet Low in Ascorbic Acid*

List 1 Foods Excluded from Diet	List 2 Only One of the Following Foods Allowed Daily
Asparagus Broccoli Brussels sprouts Cabbage Cauliflower Citrus fruits Lemons Limes Grapefruit Oranges Collards Currants Greens Mustard Spinach Turnips Green peas, fresh Horse radish Papaya Peaches, dried Peppers, green or red Pineapple Rutabagas Strawberries Tomatoes Watermelon	Apricots, dried Bananas Beef liver, cooked Blueberries Cherries, sweet Corn, sweet Cranberries Green beans Lettuce Okra Onions Radishes Sweet potatoes

choose the smallest quantity which might keep a normal person saturated on the low vitamin C diet prescribed. A barely adequate daily supplement might aid in subsequent experiments in detecting small degrees of increased requirement in persons with pathologic conditions.

The quantity of ascorbic acid in the blood plasma during fasting was measured at the onset of the experimental period and at weekly intervals thereafter. The

3 Smith, S. L. Human Requirements of Vitamin C, *J. A. M. A.* **111**: 1753 (Nov 5) 1938.

4 (a) Ralli, E. P., Friedman, G. J., and Sherry, S. The Vitamin C Requirement of Man, Estimated After Prolonged Studies of the Plasma Concentration and Daily Excretion of Vitamin C in Three Adults on Controlled Diets, *J. Clin. Investigation* **18** 708, 1939. (b) Belser, W. B., Hauck, H. M., and Storvick, C. A. A Study of the Ascorbic Acid Intake Required to Maintain Tissue Saturation in Normal Adults, *J. Nutrition* **17** 513, 1939.

macromethod of Farmer and Abt⁵ was used for all determinations. When there is a constant daily intake of ascorbic acid the level of ascorbic acid in the blood reflects the degree of saturation of the tissues with few exceptions, such as in the presence of renal damage⁶

RESULTS

Twelve persons who were attending an outpatient clinic were studied for a period of seven to eighteen weeks under the regimen previously outlined. These patients either gave no evidence of organic disease or had some pathologic condition which would not, to our knowledge, appreciably affect the requirement of vitamin C. One possible exception (patient 9) will be discussed later. Table 2 gives the pertinent data on these patients, who might be designated as a normal or "control," clinic group. The diet prior to this study appeared to have been adequate in regard to content of vitamin C for all except 3 persons (patients 1, 2 and 8). At the onset of the experiment the amount of ascorbic acid in the blood during fasting was subnormal, less than 0.4 mg per hundred cubic centimeters, in these 3 persons and in 2 others (patients 4 and 12). The minimal normal level of ascorbic acid in the blood is probably 0.4 mg per hundred cubic centimeters rather than 0.7 mg per hundred cubic centimeters, as previously accepted, since Ralli, Friedman and Sherry^{4a} have shown that normal persons given 50 mg of ascorbic acid daily are without symptoms of deficiency and maintain a concentration of plasma ascorbic acid of 0.4 mg per hundred cubic centimeters. The deficiency of vitamin C was not severe in 4 of the 5 patients in whom the level of plasma ascorbic acid was low, since saturation was achieved at the end of one week, during which time 300 mg of ascorbic acid was given daily. In each of the 7 patients in whose blood the concentration of ascorbic acid was above 0.7 mg per hundred cubic centimeters at the time of the original examination, the blood level rose at the end of one week to at least 1.4 mg per hundred cubic centimeters, which level is accepted as indicating saturation of the tissues⁷. At the end of the second week of the test period, during which 200 mg was given daily, the concentration of ascorbic acid in the blood had not increased significantly in the 11 patients who had shown a marked rise in ascorbic acid content after the first week of therapy. This was further evidence that satura-

5 Farmer, C. J., and Abt, A. F. Determination of Reduced Ascorbic Acid in Small Amounts of Blood, *Proc Soc Exper Biol & Med* **34** 146, 1936

6 Wright, I. S., and MacLenathan, E. Vitamin C Saturation. Kidney Retention After an Intravenous Test Dose of Ascorbic Acid, *Proc Soc Exper Biol & Med* **38** 55, 1938

7 (a) Van Eekelen, M. On the Amount of Ascorbic Acid in Blood and Urine. The Daily Human Requirements for Ascorbic Acid, *J Biochem* **30** 2291, 1936. (b) Faulkner, J. M., and Taylor, F. H. L. Observations on the Renal Threshold for Ascorbic Acid in Urine, *J Clin Investigation* **17** 69, 1938

TABLE 2—Ascorbic Acid in the Blood Plasma of Ambulatory Patients on a Restricted Diet Supplemented by Specified Amounts of Ascorbic Acid[†]

Patient No	Age	Weight, Pounds	Diagnosis	Previous Diet in Regard to Vitamin C	Ascorbic Acid in Blood Plasma During Fasting, Mg /100 Cc																			
					Weekly Intervals																			
					0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
1	29	97	Psychoneurosis	Fair	0.37	1.91	No med	0.89	1.05			1.35	1.19	0.90										
2	55	161	Duodenal diverticulum (asymptomatic)	Poor	0.20	1.24	1.27	0.80	0.81		0.95	1.02	1.02	0.65										
3	30	125	Psychoneurosis	Good	1.12	1.77	1.25	1.06	1.15	1.35		1.10	†			0.45	†					1.42		
4	35	180	Obesity	Good	0.08	1.62	1.50	1.03		1.32		1.10	†			0.30	†					0.74		
5	41	178	Prolapse of uterus, laceration of cervix uteri	Good	0.85	1.42	1.40	1.06	1.02		1.24	1.19	1.05	1.05										
6	15	87	Delayed puberty	Good	0.92	1.85	1.50	1.12			1.60	1.52	0.95											
7	52	135	Psychoneurosis	Good	0.92	1.86	1.96	1.70	1.62	1.75	1.65	1.56	1.84	1.75	1.62	1.27	1.42	1.27	1.65	2.17		1.57	2.05	
8	63	120	Generalized arteriosclerosis	Uncertain	0.19	0.61	0.25	0.41	0.75	1.22	Lost	1.16	1.84	1.39	1.20									
9	30	146	Oligomenorrhea, mild hypothyroidism §	Good	0.72	2.00	1.70	1.64	2.32	2.56	1.29	1.67		0.67										
10	57	136	Essential hypertension (benign)	Excellent	2.40	2.25	2.17	1.99	2.57	2.06	2.00	2.21	2.44	2.06	2.00	1.60	1.92	1.82	2.29	2.45				
11	50	143	Psychoneurosis	Excellent	1.04	2.25		1.59	1.80	1.81	1.91	2.12	1.80	1.75	1.70	1.37	1.90	1.77	1.85			2.39		
12	48	125	Essential hypertension (mild)	Good	0.17	2.41	1.89	1.41	1.62	1.22	1.75	1.27												

* Three hundred milligrams of ascorbic acid administered daily the first week, † Experimental diet resumed plus 50 mg ascorbic acid daily 200 mg daily the second week and 50 mg daily thereafter
 ‡ No ascorbic acid administered, diet unrestricted
 § Patient received 0.5 grain (0.032 Gm) of thyroid daily, but the basal metabolic rate was normal

tion had been produced. Only patient 8 failed to show a marked increase in the concentration of ascorbic acid in the blood at the end of the second week. This patient was an elderly undernourished woman with generalized arteriosclerosis, whose stores of vitamin C had evidently been markedly depleted. The slow rise in the amount of ascorbic acid in the blood may have been due in part to deficient absorption or to increased destruction in the gastrointestinal tract⁸. It was not until five weeks had elapsed that the ascorbic acid in the blood reached a normal level.

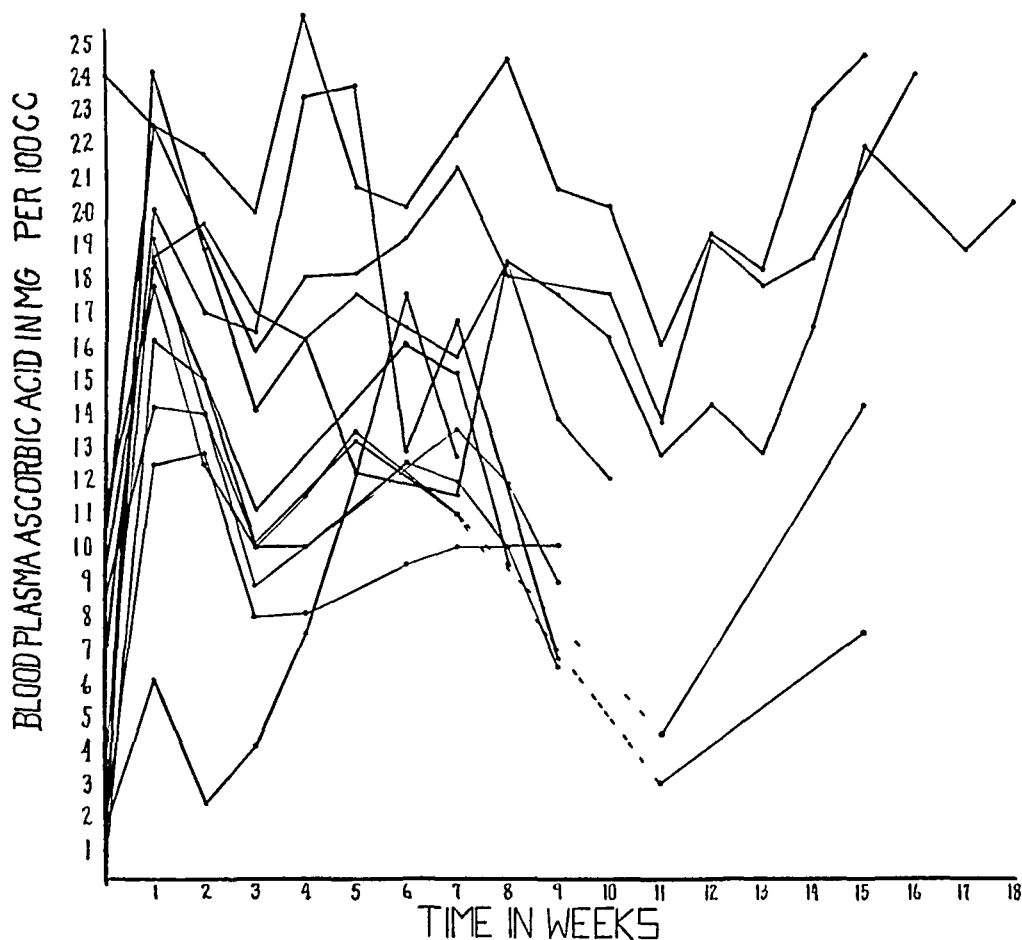
At the end of seven weeks all 12 persons showed more than 1 mg of ascorbic acid per hundred cubic centimeters of blood, which nearly all investigators would consider normal and indicative of near saturation. At the end of nine weeks, 2 of 8 patients showed a drop in the concentration of ascorbic acid in the blood to less than 0.7 mg per hundred cubic centimeters, a level considered to be suboptimal by Rall, Friedman and Sherry^{4a} and others³. One of these patients (2) was obese, and the other (patient 9) was taking 0.5 grain (0.032 Gm) of desiccated thyroid and was walking several miles each day. The human requirement of vitamin C is considered by some³ to be related to body weight, but with this Rall and her co-workers do not agree. There is some evidence that exercise increases the requirement⁸. Thyroid, by stimulating metabolism, would have a similar effect. However, the basal metabolic rate in patient 9, who was receiving desiccated thyroid, was found to vary from +4 to -2 per cent.

At the end of seven weeks 2 patients (3 and 4) were taken off medication and allowed an unrestricted diet. The concentration of ascorbic acid in the blood dropped to 0.45 and 0.30 mg, respectively, per hundred cubic centimeters at the end of four weeks. This fall was, no doubt, largely due to the fact that by this time the patients were habituated to a diet low in vitamin C and hence included few foods high in the vitamin, even when permitted to do so. When the experimental diet (low in ascorbic acid) was resumed and 50 mg of ascorbic acid again administered daily, the level of ascorbic acid in the blood rose so that at the end of four weeks it was high normal in patient 3, but it remained suboptimal in patient 4, 0.74 mg per hundred cubic centimeters. The obesity of the latter patient may have increased her requirement of vitamin C, with resultant failure of the ascorbic acid in the blood to return to a saturation level.

At the end of the experimental period the 3 patients who were observed under an uninterrupted regimen for fifteen, sixteen and eighteen weeks,

8 Hamel, P. Ueber die Vitamin C-Bilanz des Menschen. II Belastungsversuche zur Bestimmung des taglichen Verbrauches und des Sattigungsdefizits, *Klin Wchnschr* 16 1105, 1937. Belser, Hauck and Storvick^{4b}

respectively, all showed large amounts of ascorbic acid in the blood, varying from 2.05 to 2.45 mg per hundred cubic centimeters. Two of these patients (7 and 11) had multiple complaints, apparently on a psychoneurotic basis, as detailed clinical and laboratory studies, including tests of renal function, failed to show any abnormal condition. Patient 10 had essential hypertension of a moderate degree with no evidence of renal damage. As far as could be ascertained, these 3 patients observed the diet as prescribed. However, this part of the study was carried out



Ascorbic acid present in the blood plasma of ambulatory patients living on a restricted diet, and receiving daily supplements of ascorbic acid consisting of 300 mg the first week, 200 mg the second week and 50 mg thereafter

in the spring and summer, when many foods containing ascorbic acid were readily available, and there was probably some increase in the daily intake of vitamin C in the food, perhaps enough to account for the high levels found in the blood

The figure shows graphically the fluctuations in the concentration of ascorbic acid in the blood which have already been discussed. During the first two weeks of this study, the saturation period, there was a precipitous rise in the concentration of ascorbic acid in the plasma

This was followed by a drop in concentration when large daily doses of ascorbic acid were replaced by a supplement of 50 mg. After this, in spite of large fluctuations, the concentration in the blood remained about normal for a period of nine weeks in all except 2 instances. Fluctuations may have been largely due to small variations in the amount of ascorbic acid in the diet.

COMMENT

It is interesting to compare our findings with those reported in several recent investigations. Rall, Friedman and Sherry,^{4a} in a study of 3 adults on carefully controlled diets, estimated the requirement of ascorbic acid to maintain saturation to be 100 mg daily. Belser, Hauck and Stoivick,^{4b} using a saturation method in a study of 4 subjects, found the requirement for adults who weighed 60 Kg to range from 70 to more than 100 mg daily. The patients in our group received 50 mg of ascorbic acid plus that present in the diet, which was estimated to contain probably more than 20 mg a day. On this regimen, saturation was maintained in most instances.

SUMMARY

A method is described which may be used to estimate vitamin C requirement of ambulatory patients. A diet limited in ascorbic acid is prescribed, and at the end of a preliminary period, during which the body is saturated with ascorbic acid, a daily supplement of 50 mg of ascorbic acid is administered. The amount of ascorbic acid in the blood plasma is determined at weekly intervals.

In a group of 12 clinic patients who were apparently normal in regard to vitamin C nutrition, the level of ascorbic acid in the blood was maintained at or above 1 mg per hundred cubic centimeters for seven to eighteen weeks. There was some evidence that obesity increased the vitamin C requirement.

Prolonged study of the plasma ascorbic acid under a standardized regimen may prove of value in comparing the vitamin C requirement of persons with various diseases with that of the normal person.

VITAMIN C (ASCORBIC ACID) NUTRITION IN BRONCHIAL ASTHMA

AN ESTIMATION OF THE DAILY REQUIREMENT OF
ASCORBIC ACID

GRACE A GOLDSMITH, M D

ADOLPH T OGAARD, M D

AND

DONALD F GOWE, M D [†]

NEW ORLEANS

The relationship of vitamin C to hypersensitiveness has been the subject of numerous investigations in experimental animals, with conflicting and inconclusive results. The few studies of ascorbic acid and human hypersensitivity have likewise yielded divergent findings. Walzer,¹ in a recent review, concluded that no definite role for vitamin C in the immunologic mechanism of hypersensitiveness had as yet been established.

Our interest in this subject was stimulated during a study of vitamin C nutrition in the clinic and hospital population when we noted that a number of patients with bronchial asthma showed a low level of ascorbic acid in the blood plasma. Several reports of the use of ascorbic acid in the treatment of bronchial asthma have appeared, but no studies have been made of the state of vitamin C nutrition prior to therapy. Hochwald² found that ascorbic acid administered regularly was valuable in preventing symptoms of bronchial asthma and, if given intravenously in doses of 500 to 1,500 mg, was useful in aborting symptoms. Epstein³ failed to confirm these results, stating that vitamin C alone was of no help in the prevention or cure of asthmatic attacks but that it was a valuable adjuvant when used in conjunction with injections of gold salts. Hunt⁴ administered 100 mg of ascorbic acid daily to 25 patients and

[†] Formerly of New Orleans, now at St Luke's Hospital, Ponce, Puerto Rico

From the Department of Medicine, Tulane University of Louisiana School of Medicine, and the Charity Hospital of Louisiana

1 Walzer, M. A Critical Review of the Recent Literature on the Dust Atopen and on Vitamin C in Relation to Hypersensitiveness, *J Allergy* **10** 72, 1938

2 Hochwald, A, cited by Hunt ⁴

3 Epstein, A. De l'emploi de la vitamine C dans le traitement de l'asthme bronchique, *Schweiz med Wchnschr* **66** 1087, 1936

4 Hunt, H B. Ascorbic Acid in Bronchial Asthma, *Brit M J* **1** 726, 1938

obtained no effect on the severity or the incidence of attacks. Five patients obtained no relief after the intravenous injection of 500 to 800 mg of ascorbic acid, and there was no diminution in their requirements of epinephrine. Hagiesco and associates⁵ reported good or favorable results in 15 of 20 patients with bronchial asthma treated with repeated intravenous injections of 200 to 300 mg of ascorbic acid. The injections had a "suspensive action in attacks," and often after one to five injections attacks ceased or became less severe.

The purpose of this study was to determine the state of vitamin C nutrition in bronchial asthma, to learn whether or not there is an increased requirement for ascorbic acid in this condition and to determine the effect of saturation of the tissues with ascorbic acid and of the maintenance of adequate vitamin C nutrition on the number and severity of asthmatic attacks.

Thirty-two patients were studied, 9 of them over a period of eleven to thirty-five weeks. Twenty-nine of the patients had bronchial asthma, and of these, 17 had hay fever and 4 had urticaria as additional allergic manifestations. Two patients with hay fever alone and 1 with urticaria as a sole symptom were also included in this investigation. There were 2 white males, 2 Negro females and 28 white females in the group studied. The ages varied from 11 to 60 years. Although these patients were attending an outpatient clinic and belong to a low income group, the diet appeared to be varied and adequate in most instances. Twenty-three of the patients had fresh fruit and vegetables daily, which should have provided a satisfactory intake of vitamin C. In 4 instances the diet was poor, in 3 it was only fair and in 2 no dietary history was recorded. Bronchial asthma had been present for from a few weeks to twenty-six years in these patients, but in only 3 was it of less than one year's duration. The patients with hay fever had had this condition for from three to forty years. The asthma was seasonal in a few instances, but in the majority of patients it recurred throughout the year. Hypersensitivity to a wide variety of allergens was exhibited by the various patients. Asthmatic attacks were often associated with infections of the upper respiratory tract.

The amount of ascorbic acid in the blood during fasting was measured in the 32 patients, the macromethod of Farmer and Abt⁶ being used in all determinations. In the 29 cases of bronchial asthma, plasma ascorbic acid varied from 0.02 to 1.87 mg per hundred cubic centi-

5 Hagiesco, D., Bazavan, G., Criscota, M., and Cioranescu, M. *Essais de traitement de l'asthme pulmonaire par l'acide ascorbique levogyre (vitamine C)*, *Presse med* **46** 1435, 1938, abstracted, *J. A. M. A.* **111** 1885 (Nov. 12) 1938.

6 Farmer, C. J., and Abt, A. F. *Determination of Reduced Ascorbic Acid in Small Amounts of Blood*, *Proc. Soc. Exper. Biol. & Med.* **34** 141, 1936.

meters (fig 1), the mean being 0.410 ± 0.051 mg. In only 3 instances was the level in the blood above 1.0 mg, which concentration would be generally accepted as indicating excellent vitamin C nutrition. In 19 instances the ascorbic acid in the blood was less than 0.4 mg per hundred cubic centimeters, which level represents in all likelihood the low limit of normal. Ralli, Friedman and Sherry⁷ have shown that persons given 50 mg of ascorbic acid daily exhibit no symptoms of deficiency and the amount in the blood averages 0.4 mg per hundred cubic centimeters. Many previous workers have considered 0.7 mg per hundred cubic centimeters the minimal normal level of ascorbic acid in the blood.⁸ Even when the lower value of 0.4 mg is accepted, 19 of 29 patients with

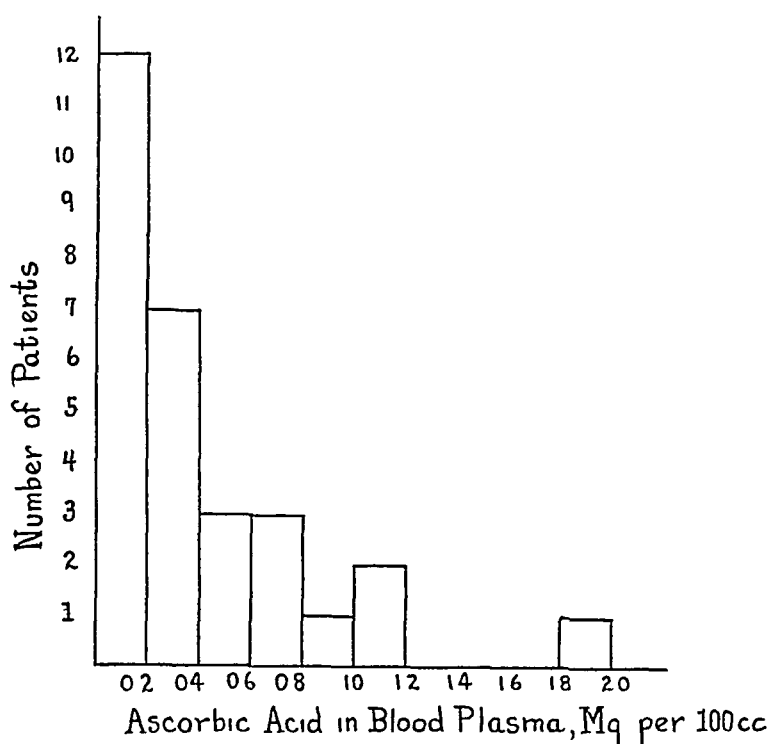


Fig 1—Distribution of the values for ascorbic acid in the blood plasma during fasting in 29 patients with bronchial asthma

bronchial asthma showed subnormal vitamin C nutrition as judged by this test. The 2 patients with hay fever only showed concentrations of ascorbic acid in the blood plasma of 0.07 and 0.08 mg per hundred cubic centimeters, and the 1 patient with urticaria alone, a level of 0.37 mg.

It is difficult to evaluate the foregoing findings, which show such a high incidence of vitamin C deficiency in a group of patients with asthma

7 Ralli, C. P., Friedman, G. J., and Sherry, S. The Vitamin C Requirement of Man, Estimated After Prolonged Studies of Plasma Concentration and Daily Excretion of Vitamin C in Three Adults on Controlled Diets, *J. Clin. Investigation* **18** 705, 1939.

8 Smith, S. L. Human Requirements of Vitamin C, *J. A. M. A.* **111** 1753 (Nov. 5) 1938.

The deficiency could be etiologically related to bronchial asthma, or it could be the result of the asthmatic seizures. An increased requirement for ascorbic acid would explain the findings, or the deficiency might be entirely unrelated to the allergic manifestations. Poor absorption from the gastrointestinal tract could account for the deficiency. It seemed unlikely that an inadequate intake of vitamin C was the complete explanation of the foregoing observations in view of the good dietary history of most of the patients. It is, of course, recognized that such histories are often inaccurate.

Determination of the frequency with which vitamin C subnutrition occurred in the general clinic population would aid in the interpretation of the data for patients with asthma. The amount of ascorbic acid in the blood plasma was measured in a number of persons attending the outpatient clinic who had no condition known to be associated with subnormal vitamin C nutrition. Patients with infection, hypermetabolism, diarrhea, ulcer or definite deficiency syndromes were excluded from consideration. Diagnoses in this control group included psychoneurosis, hypertension, compensated cardiac disease, obesity, hookworm infection and diabetes. The ascorbic acid in the blood plasma in 43 patients with such conditions varied from 0.07 to 2.40 mg per hundred cubic centimeters, with a mean value of 0.602 ± 0.049 mg. As previously stated, the mean for the level of ascorbic acid in 29 persons with asthma was 0.410 ± 0.051 mg per hundred cubic centimeters. The difference between these two means is 0.192 ± 0.070 . This difference is seen to be 2.7 times the probable error, which may or may not be significant. A larger number of persons will have to be studied for definite evaluation of these results. The findings, however, suggest that the low levels of ascorbic acid in this group of persons with bronchial asthma may be dependent on factors other than an inadequate diet.

Further studies were made on a few of the patients with asthma. Five were given intravenous tolerance tests to determine the degree of saturation of the body with vitamin C. The results are indicated in figure 2. The normal response to 1.0 Gm of ascorbic acid administered intravenously is the excretion of 400 mg or more in the urine in the subsequent five hours⁹ or an increase in the ascorbic acid of the blood plasma to at least 7.0 mg per hundred cubic centimeters in twenty minutes, a minimum level of 2.5 mg being found at the end of two hours and of

9 (a) Wright, I. S., Lilienfeld, A., and MacLenathen, E. Determination of Vitamin C Saturation. A Five Hour Test After an Intravenous Test Dose, *Arch Int Med* **60** 264 (Aug.) 1937. (b) Portnoy, B., and Wilkinson, J. Vitamin C Deficiency in Peptic Ulcer with Hematemesis, *Brit M J* **1** 554, 1938. (c) Goldsmith, G. A., Ogaard, A. T., and Gowe, D. F. Vitamin C Nutrition in Pellagra, *Am J M Sc* **200** 244, 1940.

1.6 mg at the end of four hours^{9c} In 2 patients vitamin C nutrition appeared normal, since they excreted more than 400 mg of ascorbic acid in the urine in five hours, but in only 1 of these persons was a normal elevation of ascorbic acid in the blood attained This discrepancy might denote a low renal threshold for ascorbic acid in this patient, and, if this is the correct explanation, vitamin C subnutrition would be indicated On the other hand, normal tissue saturation with the vitamin may have been present and some error made in determination of the ascorbic acid in the blood In 3 patients the results of the intravenous tolerance test indicated definite vitamin C deficiency of the tissues

Seven patients with bronchial asthma, 5 of whom had hay fever as well, 1 patient with hay fever only and 1 patient with urticaria of unde-

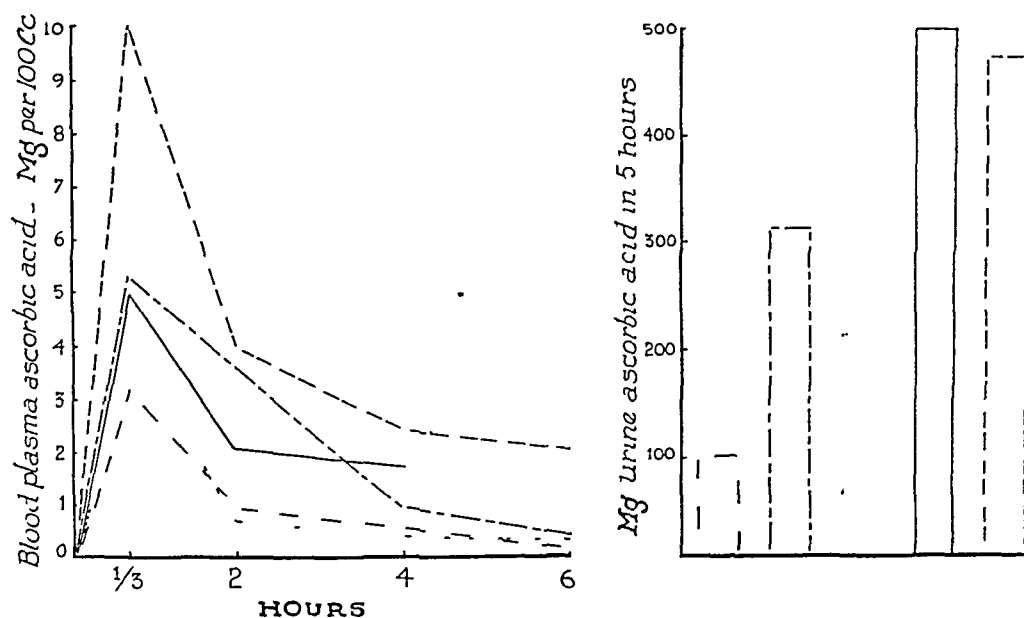


Fig 2—Results of intravenous tolerance tests of vitamin C nutrition in patients with bronchial asthma

terminated cause were studied over a long period to determine whether or not there was an increased requirement for vitamin C The method used was described by us in a previous paper in which the study of a "control" group of persons attending an outpatient clinic was reported¹⁰ Briefly, it is as follows A diet low in ascorbic acid is prescribed, and the subject is saturated with vitamin C by the administration of 300 mg of ascorbic acid daily for one week¹¹ and 200 mg daily for a second week After this, 50 mg of ascorbic acid is given per day throughout the experimental period The amount of ascorbic acid in the blood plasma during

10 Goldsmith, G A , Ogaard, A T , and Gowe, D F Estimation of Ascorbic Acid (Vitamin C) Requirement of Ambulatory Patients, *Arch Int Med*, this issue, p 590

11 Ascorbic acid was supplied by Merck & Co, Inc

fasting is determined at weekly intervals. The accompanying table shows the results of this study. At the beginning of the experiment 4 of the 7 patients with bronchial asthma showed extremely low levels of ascorbic acid in the blood, that is, it was less than 0.2 mg per hundred cubic centimeters, which is the amount one would expect to find in persons with scurvy. After the first week of medication the amount of ascorbic acid in the blood had increased to more than 1.2 mg per hundred cubic centimeters, indicating approximate saturation of the body with this substance, in all cases except 1 (patient 5), in which the level

Ascorbic Acid in the Blood Plasma of Patients with Bronchial Asthma on

Number	Age	Weight, Pounds	Diagnosis	Diet in Regard to Vitamin C	Fast mg	Ascorbic Acid in									
						1	2	3	4	5	6	7	8	9	10
1	31	185	Bronchial asthma, hay fever	Poor	0.15	1.21	1.50		No medi- cation	0.78	1.51	1.56	1.36	0.62	0.86
2	41	170	Bronchial asthma, hay fever	Poor	0.16	1.60	1.72	0.99	0.58		0.27	0.41	0.45		0.52
3	26	135	Bronchial asthma	Good	0.17	1.80	1.79	1.50	0.71	0.52		0.46	0.54	0.51	0.37
4	43	198	Bronchial asthma, hay fever	Good	0.44	1.57	1.62	1.30		0.85	0.81	0.85	0.49	0.60	0.60
5	43	205	Bronchial asthma	Fair	0.67	0.90†		1.04	0.99	0.80	0.75			0.75	0.56
6	46	147	Bronchial asthma, hay fever	Good	0.17	1.24	1.35	1.38	0.77				0.57	0.62	0.66
7	20	110	Bronchial asthma, hay fever	Good	0.52	2.06	1.52	1.45	1.50	1.47	1.55	1.54	1.64	0.87	1.40
8	27	105	Hay fever	Fair	0.08	2.51	2.27	1.96	1.06	1.46	1.10	1.40	1.62	1.17	1.40
9	58	120	Urticaria	Fair	0.37	0.82	1.42			Lost		1.20			1.44

* Three hundred milligrams of ascorbic acid administered daily the first week, 200 mg daily the second week and 50 mg daily thereafter.

† Resaturation with ascorbic acid by administration of 200 mg daily for two weeks and 100 mg daily thereafter.

‡ One hundred milligrams of ascorbic acid administered daily for two weeks.

was 0.90 mg. Poor intestinal absorption or a marked vitamin C deficiency could explain the delayed rise in ascorbic acid in this 1 case. At the end of the second week of vitamin therapy there were a small increase in the ascorbic acid in the blood in 4 instances and a slight drop in 2. The amount of ascorbic acid in the blood was above 1.35 mg per hundred cubic centimeters in each patient, indicating that the tissues were fairly well saturated with vitamin C. One (patient 5), through a misunderstanding, took 100 mg of ascorbic acid daily for the second and third weeks of the experiment instead of the prescribed amount, and the level of ascorbic acid in the blood never rose above 1.04 mg per hundred cubic centimeters. In 5 of the 7 asthmatic patients plasma ascorbic acid gradually decreased, so that at the end of seven weeks

the level was considerably less than 1.0 mg per hundred cubic centimeters. The findings are shown graphically in figure 3.

A similar study of a control group of 12 persons showed that after the same interval of time, namely, seven weeks, a level of more than 1.0 mg per hundred cubic centimeters of blood was maintained in each instance.¹⁰ At the end of the ninth week all of the patients with bronchial asthma showed less than 1.0 mg of ascorbic acid per hundred cubic centimeters of blood, but in 1 instance this drop was only temporary. In the control group, only 2 had shown a similar fall at the end of nine

*a Restricted Diet Supplemented by Specified Amounts of Ascorbic Acid **

Blood Plasma During Fasting, Mg /100 Cc, Measured at Weekly Intervals																					
11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
0.67	0.59		0.85	0.42	0.62	0.75	0.46	0.31†	1.76	1.59		0.97	0.56		0.62		0.94		0.65	0.35	
0.50			0.19			0.17															
0.85				0.12	0.21			0.15	0.21†	1.80	1.16		1.34			1.09			1.32	1.50	
	0.79	0.61	0.61	0.91†	1.80		1.52		1.26			1.25	1.15	0.92		0.82		1.17			
0.31																					
0.52	0.74	1.01	0.61	0.88	0.75	†	1.10	0.97			1.17	1.35		0.75	0.92		1.81	1.02			
1.51	1.80	1.90	1.86	1.72	1.70		1.92			2.27											
1.49		1.57	1.36	1.41	1.65		1.34	1.90	1.65	1.64	1.59	1.64	1.44				1.57	2.21	1.65	2.18	2.12
			1.22				0.59														

weeks. In 4 patients with asthma the decrease in ascorbic acid in the blood continued, so that patient 1 had a level of 0.31 mg per hundred cubic centimeters at the end of nineteen weeks, patient 2 had a level of 0.17 mg after seventeen weeks, patient 3 had a level of 0.21 mg after twenty weeks and patient 5 had a level of 0.31 mg at the end of the eleven weeks. In patients 4 and 6 the amount of ascorbic acid in the blood ranged between 0.6 and 0.9 mg per hundred cubic centimeters. Only patient 7 maintained a normal level in the blood throughout the experimental period. Five normal patients were observed for fifteen to eighteen weeks. In all except 1 the level in the blood remained above 1.42 mg, and in that instance there had been an interval of one month between the seventh and the eleventh week in which no ascorbic acid had been administered.

The fact that patients with asthma failed to maintain as high a level of ascorbic acid in the blood as did a control group under a similar regimen appears to indicate an increased requirement of vitamin C in patients with bronchial asthma. Failure of absorption of ascorbic acid from the gastrointestinal tract does not seem to be a likely explanation of the findings, since saturation of the body by oral administration was obtained as readily in patients with asthma as in members of the control group.

Four of the patients with asthma were resaturated with ascorbic acid at the end of fifteen to twenty weeks by the administration of 200 mg daily for two weeks. After this a maintenance dose of 100 mg a day was instituted and the diet continued. With this daily supplement, 3 of the 4 persons studied maintained for ten or more weeks a level of ascorbic

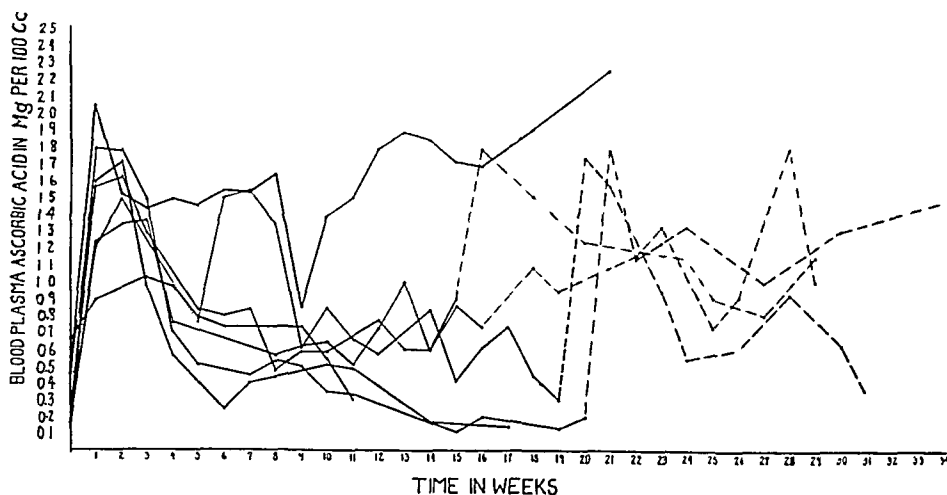


Fig 3—Ascorbic acid in the blood plasma of patients with bronchial asthma on a restricted diet supplemented by ascorbic acid. Solid lines indicate ascorbic acid levels during a two weeks period of saturation (300 mg of ascorbic acid daily the first week, 200 mg daily the second week) followed by the administration of 50 mg daily. Broken lines indicate ascorbic acid levels during resaturation with the substance (200 mg daily for two weeks) followed by administration of 100 mg daily.

acid in the blood which tended to be above 1.0 mg per hundred cubic centimeters. The occurrence of pregnancy in the fourth patient was, no doubt, a contributory factor in the decrease of ascorbic acid in the blood which was observed.

The patient whose only allergic manifestation was hay fever was able to maintain a high level of vitamin C in the blood for thirty-two weeks while receiving 50 mg of ascorbic acid daily. The person with urticaria showed a gradual decrease in plasma ascorbic acid to 0.59 mg per hundred cubic centimeters at the end of the eighteenth week. Her condition was improved during the period in which the level of ascorbic acid in

the blood was over 1.0 mg. Rosenberg¹² found a subnormal amount of ascorbic acid in the blood in 7 cases of urticaria. Therapy with citrus fruits resulted in benefit in each instance.

During the entire experimental period of several months, each patient was studied from the standpoint of the number and severity of asthmatic attacks. An attempt was made to determine whether or not there was any relationship between the amount of ascorbic acid in the blood and the asthmatic seizures. It was necessary at times for the patient to take epinephrine, ephedrine or aminophylline for relief of the asthma. These drugs did not appear to influence the amount of ascorbic acid in the blood. Two patients were almost free from symptoms throughout this study. Patient 2 had only one asthmatic attack during seventeen weeks of observation. However, it is not justifiable to ascribe her well-being to the regimen outlined, since her asthma had always occurred largely in the fall in association with hay fever. She was studied from December to April and might have been free of attacks irrespective of type of therapy. Patient 3 had no asthma for thirty-five weeks. Her symptoms were of recent origin, and the first asthmatic attack occurred only a few weeks before this study was instituted, hence her freedom from symptoms may have been unrelated to the experimental regimen. Patients 1, 4, 5 and 6 all had severe asthma of long duration prior to this investigation. Attacks had occurred almost daily, and ephedrine, epinephrine or aminophylline was used for relief. Patient 1 had had almost continuous asthma for four weeks prior to the institution of therapy with ascorbic acid. After the second week of this study, at which time the ascorbic acid in the blood reached 1.5 mg. per hundred cubic centimeters, she was free of attacks for five weeks, then one asthmatic seizure occurred. The plasma ascorbic acid, which was at this time 1.56 mg. per hundred cubic centimeters, fell gradually to 0.31 mg. at the nineteenth week. She was, however, symptom free until the twelfth week, when a visualization of the gallbladder was performed. The ingested dye initiated a series of asthmatic attacks, which continued until the twentieth week. During this interval the patient became pregnant, which may have partially accounted for a change in the number of asthmatic attacks as well as for the diminution of ascorbic acid in the blood. At the twentieth week she was given 200 mg. of ascorbic acid daily for two weeks and 100 mg. daily thereafter, with the result that the body was again saturated with vitamin C, the level of ascorbic acid in the blood reaching 1.5 mg. per hundred cubic centimeters. The asthmatic attacks ceased until the twenty-fourth week, when she had several mild seizures. The

12 Rosenberg, W. A. Vitamin C Deficiency as a Cause of Urticaria, *Arch Dermat & Syph* 37:1010 (June) 1938

level of ascorbic acid in the blood had decreased to 0.56 mg per hundred cubic centimeters. In the next four weeks she had only one slight seizure, and the plasma ascorbic acid rose to 0.94 mg. In the thirtieth week she again had several asthmatic attacks, and there was a concomitant drop in the level of ascorbic acid in the blood. Although this level continued to fall, she remained free of attacks during the thirty-first week.

Patient 4 had daily attacks of asthma before and during this period of study. They were especially severe in the seventh to the tenth week, at which time the level of ascorbic acid in the blood was lower than that previously observed. After the fifteenth week the patient was resaturated with ascorbic acid by taking 200 mg of the substance daily for two weeks, and 100 mg for the remainder of the experiment. She was free of asthma for eight weeks, but from the twenty-fourth to the twenty-seventh week she had two or three mild attacks weekly. At this time there was a slight fall in the concentration of ascorbic acid in the blood. In the last three weeks of the study slight edema on the basis of chronic nephritis also developed.

Patient 5 had frequent asthmatic attacks, which were not changed either in frequency or in severity in any way during the period of observation. The level of ascorbic acid in the blood in this patient was never elevated to more than 1.04 mg per hundred cubic centimeters.

Patient 6 stated that after the institution of ascorbic acid therapy her asthmatic attacks became less severe, but that the frequency was unaffected, except that from the tenth to the twelfth week of observation she had no seizures. During this interval the ascorbic acid in the blood was definitely subnormal, a finding at variance with the results for the other patients already discussed. After the twelfth week asthmatic seizures of varying intensity again occurred at frequent intervals.

Although patient 7 was observed for twenty-one weeks, she had only two mild asthmatic attacks. She stated that her usual fall hay fever, which appeared while she was being studied, was less severe than in the preceding year. The ascorbic acid level in the blood remained high throughout the experimental period.

In summary, there appeared to be some relationship in patients 1 and 4 between the level of ascorbic acid in the blood and the asthmatic attacks. When seizures were frequent the ascorbic acid in the blood was usually found to be low. This decrease may have been either the result of attacks or a condition etiologically related to them, but the former appears more likely. Patients 1 and 4 also seemed to show definite improvement when the body was saturated with vitamin C. A relatively large amount of vitamin C in the body tissues was of possible but doubtful benefit in 4 other patients. The status of the remaining

patient was unchanged during the period of observation, but saturation of the body with ascorbic acid was not maintained for any period of time.

A few of the findings in 6 additional patients who could not be included in the study reported here, either because of failure to follow the outlined regimen or because of cooperation for only a short interval, are worthy of comment. One patient who was observed for five weeks showed a drop in the level of ascorbic acid in the blood from 1.25 mg after saturation to 0.9 mg per hundred cubic centimeters and experienced more asthmatic attacks at the latter level. Another patient was free of seizures for three weeks, during which time the level of ascorbic acid in the blood was above 1.0 mg. One attack occurred during the fourth week, and the level of plasma ascorbic acid was found to be 0.72 mg. There was again a rise, so that at six weeks the amount in the blood was 1.05 mg per hundred cubic centimeters. In a third patient, who was seen for only three consecutive weeks, the ascorbic acid in the blood measured 1.20 mg per hundred cubic centimeters at the second week and 0.77 mg at the third week, a rapid fall. His asthma was extremely severe and was not improved when the body was saturated with vitamin C. Two patients were observed for a number of weeks, but failed to follow the prescribed diet or to take the medicament regularly. In both of them the ascorbic acid in the blood was always above 1.0 mg per hundred cubic centimeters. One patient reported a diminution in the severity of the asthma while she was taking ascorbic acid, the other experienced no effect. An interesting finding was reported by a sixth patient with severe asthma. She stated that after receiving 300 mg of ascorbic acid daily for a week she was able to sleep for the first time in months. During this time the level of ascorbic acid in the blood rose from 0.62 to 1.60 mg per hundred cubic centimeters.

Ascorbic acid was injected intravenously in doses of 1 Gm to 2 patients during acute attacks of bronchial asthma. One patient, whose asthmatic attack had lasted forty-eight hours and had been unaffected by epinephrine, ephedrine or aminophylline, was free of symptoms for twenty-four hours after the injection of ascorbic acid. The other patient obtained temporary relief, which lasted only a few hours after the intravenous therapy.

COMMENT

The data presented indicate that there may be an increased requirement of vitamin C in patients with bronchial asthma. It is interesting to speculate in regard to the cause of such an increase. The organism appears to need more ascorbic acid in states of heightened metabolism. There is some evidence that exercise increases the requirement. The labored breathing during asthmatic attacks involves considerable muscular effort and might also cause a temporary elevation in the metabolic

rate Harrison¹³ has shown that the labored breathing associated with the dyspnea of heart failure is one factor in the production of an elevated basal metabolic rate in that condition. There have been numerous reports which indicate that in infections the ascorbic acid requirement is increased. This increase may not be entirely due to fever, since even in chronic infections, such as sinusitis, vitamin C subnutrition may be found. Asthma appears at times to be closely related to infection, which may be localized primarily or secondarily in the bronchi or may be present in some focus elsewhere in the body.

Possibly an increased need of ascorbic acid in asthma is intimately related to the allergic reaction, although no conclusive data can be cited in this regard. It is also possible that the apparent increase in vitamin C requirement in the group of patients with asthma included in this report was unrelated to the asthmatic state and dependent entirely on extraneous factors.

SUMMARY

The amount of ascorbic acid in the blood plasma during fasting averaged 0.410 ± 0.051 mg per hundred cubic centimeters in 29 persons with bronchial asthma, a subnormal level being found in 19 instances. The mean level of ascorbic acid in a comparable "control" group of 43 patients was 0.602 ± 0.049 mg per hundred cubic centimeters.

During a period of several months on a standardized regimen, 6 of 7 patients with bronchial asthma were unable to maintain a level of ascorbic acid in the blood of 1.0 mg per hundred cubic centimeters or more, whereas members of a control group previously studied under the same regimen maintained such a level in most instances. This is interpreted as indicating an increased requirement of vitamin C in the patients with asthma.

There appeared to be some relationship between the amount of ascorbic acid in the blood and the frequency and severity of asthmatic attacks in 2 patients. When the body was saturated with ascorbic acid the condition of these persons was much improved. In 5 other patients the asthma was not influenced appreciably by the administration of ascorbic acid and any beneficial effect noted was probably nonspecific.

13 Harrison, T. R. *Failure of the Circulation*, Baltimore, Williams & Wilkins Company, 1939, p. 309.

JEJUNAL (ANASTOMOTIC) ULCER

A CLINICAL AND PATHOLOGIC STUDY WITH REPORT OF
EIGHT CASES ENCOUNTERED IN 13,000 NECROPSIES

M M MONTGOMERY, M D

AND

J D KIRSHBAUM, M D

CHICAGO

In recent years there have been many contributions to the literature on gastrojejunal, or anastomotic, ulcer. However, few studies of the lesion as encountered during postmortem examination have been reported. Our study concerned 8 cases observed in a series of 13,000 consecutive necropsies performed from 1929 to 1940 at the Cook County Hospital. Two of our cases were included in a paper by Portis and Jaffé¹

Primary jejunal ulcer is rare. Judd² in 1921 stated he had never seen a case and questioned its occurrence. Ebeling³ in 1933, under the title of "Primary Jejunal Ulcer," reported a case in which diagnosis was made by roentgen examination prior to operation and enumerated 46 other cases reported from 1827 to 1932. However, the ulcers in these cases were primary in the sense that they were not secondary to gastrojejunostomy. The author expressed the belief that the primary etiologic agent of jejunal ulcer included typhoid fever, bacillary or amebic dysentery and possibly syphilis. Misplaced gastric mucosa has been suggested as the etiologic basis in some cases. In many of the earlier cases the condition was reported as peptic ulcer, but this diagnosis is open to question.

Jejunal or gastrojejunal ulcer is practically always secondary to an anastomosis between the stomach and the jejunum, with or without gastric resection. This ulcer may not appear for many years, and for this reason fewer persons suffer from the lesion at any one time than one would expect from the reported incidence. No doubt this explains its relatively rare occurrence in this series of necropsies.

The lesion may be confined to the jejunum, or it may involve the margins of the stoma or the gastric mucosa, in which case it may be referred to as a gastrojejunal, or marginal, ulcer.

From the Department of Pathology, Cook County Hospital, and the Department of Medicine, University of Illinois

1 Portis, S. A., and Jaffe, R. H. Study of Peptic Ulcer on Necropsy Records, *J. A. M. A.* **110** 6 (Jan 1) 1938

2 Judd, E. S. *Surg., Gynec. & Obst.* **33** 120, 1921

3 Ebeling, W. W. *Ann. Surg.* **97** 857, 1933

The history of the knowledge of gastrijejunal ulcer is intimately associated with the development of gastroenterostomy. This operation was first performed by Wolfer⁴ in 1881. He had operated for a carcinoma of the pylorus, intending to resect the tumor by one of Billroth's methods, however, the tumor was fixed, and there were metastases in the liver. Nicoladini, his assistant, cited by Moynihan,⁵ suggested that the obstruction could be relieved by anastomosing the stomach and the bowel. This procedure was carried out, with excellent results. A short time later Wolfer used the same method of treatment for pyloric obstruction due to a benign ulcer. This operation soon became popular. It was not until 1889 that Brown⁶ reported the first case of peptic jejunal ulcer. This developed about one year after operation. The first case in the French literature was recorded by Quénu in 1902.⁷ Robson⁸ in 1904 reported the first case in the English literature.

Key⁹ in 1907 reviewed 55 cases in the literature. Moynihan¹⁰ in 1908 reviewed 60 cases and stressed the fact that diagnosis was difficult except at operation or necropsy. Deaver and Ashhurst¹¹ in 1909 reported 10 cases of jejunal ulcer among 1,198 gastroenterostomies, an incidence of less than 1 per cent. However, information concerning the "follow-up" of these cases was not given. Paterson¹² in 1909 collected records of 65 cases of jejunal ulcer and stated that the lesion did not occur after posterior no loop gastroenterostomy. Von Eiselsberg¹³ in 1914, Judd¹⁴ in 1921 and Moynihan¹⁵ in 1923 estimated the occurrence at 1 or 2 per cent. However, as Judd pointed out, the method of computation was inaccurate, since it accounted only for those patients returning to the original operator with jejunal ulcer. Other factors influenced the statistics. A patient with mild symptoms might not seek treatment. Small ulcers were no doubt often overlooked. The patient often went elsewhere for treatment. Frequently sufficient time had not elapsed

4 Wolfer. *Centralbl f Chir* **45** 705, 1881.

5 Moynihan, B. G. A. *Abdominal Operations*, ed. 4, Philadelphia, W. B. Saunders Company, 1926, p. 224.

6 Brown. *Verhandl d deutsch Gesellsch f Chir* **2** 94, 1889.

7 Quénu. *Bull et mém Soc de chir de Paris* **28** 250, 1902.

8 Robson, A. W. M. *Ann Surg* **40** 201, 1904.

9 Key, E. *Nord med ark* (pt 1) **7** 1, 1907.

10 Moynihan, B. G. A., cited by Deaver and Ashhurst,¹¹ p. 431.

11 Deaver, J. B., and Ashhurst, A. P. C. *Surgery of the Upper Abdomen*, Philadelphia, P. Blakiston's Son & Co., 1909, p. 459.

12 Paterson, H. J. *Ann Surg* **50** 367, 1909.

13 von Eiselsberg, F. *M. Press* **98** 196, 1914.

14 Judd, E. S. *Surg, Gynec & Obst* **33** 120, 1921.

15 Moynihan, B. G. A. *Lancet* **1** 631, 1923.

since the gastroenterostomy for the development of the ulcer. Finally, the number of cases in any series increased over a period of years, this is well shown in our few cases.

Beer¹⁶ in 1923 reported 62 cases in which gastrojejunostomy was performed for the relief of gastric and duodenal ulcer. The patients had been followed from two to eleven years, and jejunal ulcer had been diagnosed in 4 cases, an incidence of 6.4 per cent. As the patients were followed over a longer period the incidence rose. Bastianelli¹⁷ in 1927 reported an incidence of 24 per cent. The figure recorded by Strauss, Block and Freidman¹⁸ in 1928 was 25 per cent.

This increasing incidence was influenced by the increasing frequency with which the operation was used in the treatment of duodenal ulcer, its diminishing use in the treatment of gastric ulcer and the passage of time, since in some cases the condition developed ten to fifteen years after the operation. More frequent use of roentgen examination in diagnosis no doubt was another factor.

The earlier operations were done for ulcer of the stomach, in which condition the degree of acidity is usually less than in ulcer of the duodenum. It is well known that the greater the degree of acidity, the more probable is the development of jejunal ulcer. For example, operations for carcinoma of the stomach are practically never followed by this lesion. Balfour¹⁹ in 1925 reported that the occurrence of jejunal ulcer was twenty times more common after an operation for duodenal ulcer than one for gastric ulcer. Von Hoberer²⁰ reported a marked increase in the incidence of jejunal ulcer when there was benign pyloric obstruction. The acidity of the gastric contents in the unobstructed organ is lowered by regurgitation of the alkaline duodenal contents through the pylorus. This is less likely to occur in cases of resection with closure of the proximal end of the duodenum and the distal end of the stomach and gastrojejunostomy. We had 2 cases of such a condition.

Hurst and Stewart²¹ called attention to the fact that although a large majority of anastomotic ulcers follow gastrojejunostomy, they may occur after every type of partial gastrectomy with an anastomosis. They cited 67 cases collected by Birgfeld²² from the German literature.

16 Beer, T. *Deutsche Ztschr. f. Chir.* **137** 1, 1923.

17 Bastianelli, R., cited by Hurst and Stewart,²¹ p. 453.

18 Strauss, A. A., Block, L., and Freidman, J. G. *Gastro-Jejunal Ulcer: Medical and Surgical Considerations*, J. A. M. A. **90** 181 (Jan. 21) 1928.

19 Balfour, D. C. *Ann. Surg.* **82** 421, 1925.

20 von Hoberer, H. *Arch. f. klin. Chir.* **119** 712, 1922.

21 Hurst, A. F., and Stewart, M. J. *Gastric and Duodenal Ulcer*, New York: Oxford University Press, 1929, p. 455.

22 Birgfeld, E. *Arch. f. klin. Chir.* **137** 568, 1925.

in 1925 and added 30 more reported from 1925 to 1927 in which an anastomotic ulcer followed gastrectomy. They reported 3 cases in which a gastrojejunal ulcer developed after resection of the greater part of the stomach for an anastomotic ulcer which had developed after gastroenterostomy. Gatewood²³ in 1930 noted 3 anastomotic ulcers in 30 resections done since 1915, an incidence of 10 per cent.

Lahey and Swenton²⁴ in 1935 stressed the fact that "gastrojejunal ulcer is now considered a serious and not unlikely complication of any operative procedure for ulcer in which the stomach is anastomosed to the jejunum and not a sequela peculiar only to gastroenterostomy." This possibility has been stressed in the literature during the past few years, and many authorities have advised more radical resection.

REPORT OF CASES

CASE 1—T. R., a white man aged 50, had a gastric resection with closure of the distal end of the stomach and gastrojejunal anastomosis seventeen years prior to the onset of the present illness. For the past ten years he had been drinking heavily. There was complete relief from symptoms referable to the gastrointestinal tract until six weeks before his admission to the hospital, when he noted the onset of weakness and marked pallor and passed tarry stools. After a few days he felt better and had apparently recovered, when he suddenly collapsed and later passed tarry stools. On entrance to the hospital he was well nourished but pale. His pulse rate was 100 per minute, his respiratory rate 24 per minute and his blood pressure 144 systolic and 94 diastolic. His hemoglobin concentration was 30 per cent and his red cell count 1,930,000 per cubic millimeter.

Clinical Diagnosis—The clinical diagnosis was a hemorrhaging marginal ulcer. The patient was placed on a conservative regimen and was apparently improving, when he suddenly complained of air hunger and the pulse became imperceptible. He died three days after his entrance into the hospital.

Essential Anatomic Findings—Two peptic ulcers occurred in the proximal portion of the jejunum, adjacent to a gastrojejunostomy stoma. There was appreciable bleeding from an open blood vessel in the base of one of the ulcers. Hemorrhagic jejunitis with tarry intestinal contents, distinct anemia, partial gastric resection and gastrojejunal anastomosis were observed. The ulcers measured 8 by 5 mm and 15 by 10 mm, respectively. Each was about 1 mm in depth, with firm edges. The lumen of the open blood vessel in the base of the larger ulcer measured less than 1 mm in diameter.

CASE 2—L. B., a white man aged 42, was operated on twenty-one years prior to admission for a "ruptured stomach." At that time the perforation was closed, and a gastrojejunostomy was performed. He had no pain in the interval but had some distention after the ingestion of certain foods. About thirty-six hours before his entrance into the hospital he experienced a sudden, sharp, excruciating pain in the epigastrium. This was severe and was unrelieved by medicine given him by his physician. He vomited several times. On entrance the temperature

23 Gatewood. *Ann Surg* 92:554, 1930.

24 Lahey, F. H., and Swenton, N. W. *Surg, Gynec & Obst* 61:599, 1935.

was 103.8 F, the pulse rate 136 per minute, the respiratory rate 40 per minute and the blood pressure 120 systolic and 80 diastolic. His abdomen was slightly distended and rigid, and peristaltic sounds were absent.

Clinical Diagnosis—The clinical diagnosis was generalized peritonitis secondary to a ruptured peptic ulcer. The patient was treated conservatively. He died thirty hours after admission to the hospital.

Essential Anatomic Findings—A perforated peptic ulcer of the jejunum with diffuse fibrinopurulent peritonitis and evidences of an old posterior gastrojejunostomy were observed. The ulcer, located opposite the stoma, measured 15 by 20 mm and extended deep into the jejunal wall. In the base there was an opening, measuring 5 by 7 mm and communicating with the peritoneal cavity.

CASE 3—S. P., a white man aged 51, was known to have a peptic ulcer. For the past ten years he had attended the clinic for gastrointestinal diseases. Six weeks prior to death the patient had an exclusion operation, and a gastrojejunal anastomosis was performed because of bleeding and pain which occurred despite medical treatment. Two weeks before his death severe pain developed in the right upper quadrant of the abdomen, and the patient reentered the hospital. His temperature was 99.8 F, his pulse rate 92 per minute, his respiratory rate 20 per minute and his blood pressure 128 systolic and 76 diastolic. There was tenderness in the epigastric region.

Clinical Diagnosis—The clinical diagnosis was marginal ulcer with post-operative adhesions. The patient was transferred to a surgical ward a day after entrance because of exacerbation of symptoms, but was treated conservatively because of his poor condition. He died two weeks after his acute symptoms appeared and six weeks after gastrojejunostomy was performed.

Essential Anatomic Findings—A perforated peptic ulcer in the proximal portion of the jejunum with localized suppurative peritonitis and a recent gastrojejunostomy wound were observed. Pronounced coronary sclerosis with fibrosis in the region of the apex and the left portion of the interventricular septum was present. The stomach had been sutured across so that the distal half communicated with the duodenum and the proximal half was anastomosed with the jejunum. An annular ulcer scar in the proximal portion of the duodenum constricted the lumen to 35 mm in circumference. The jejunal ulcer was located 9 cm below the stoma, in the distal limb of the jejunum, and measured 32 by 10 mm. The edges were sloping. The perforation measured 9 by 9 mm.

CASE 4—J. O'M., a white man aged 60, had been troubled with epigastric pain for many years. He had had a gastrojejunostomy performed nine years before his terminal admission to the hospital, but this did not relieve his symptoms. He was an addict to the use of alcohol and barbitals. He was admitted to the hospital in a comatose state. His temperature was 101 F, his pulse rate 94 per minute, his respiratory rate 28 per minute and his blood pressure 120 systolic and 82 diastolic. There were rales over the bases of both lungs posteriorly.

Clinical Diagnosis—The clinical diagnosis was barbitals poisoning and bronchopneumonia. The patient died forty-eight hours after his entrance into the hospital.

Essential Anatomic Findings—A chronic peptic ulcer of the jejunum occurred below a gastroenteroanastomosis. Confluent bronchopneumonia of the lower lobes of both lungs was observed, with gangrene beginning in the lower lobe of the right lung. Chemical examination of the liver revealed 1 grain (0.06 Gm) of a barbiturate in each 320 Gm of liver. The jejunal ulcer was located opposite the stoma and measured 30 by 22 mm. In the duodenum, there were two dark brown scarred areas, representing healed ulcers.

CASE 5—G G, a white man aged 40, gave a history of symptoms of ulcer of many years' duration. Eleven years before his admission to the hospital gastrojejunostomy was performed for an acute perforated ulcer. He was relieved completely of his symptoms until three months before admission, when abdominal pain developed and became progressively worse. A sudden excruciating pain was felt four hours prior to his entrance into the hospital. On entrance he appeared to be in shock. His temperature was 99.4 F, his pulse rate 150 per minute and his respiratory rate 30 per minute. His abdomen was rigid, and peristaltic sounds were absent.

Clinical Diagnosis—The clinical diagnosis was perforated peptic ulcer. At operation, a large gastrojejunal ulcer with perforation was found. About 3,000 cc of fluid was aspirated from the abdominal cavity. The patient died on the nineteenth day after operation.

Essential Anatomic Findings—The recent surgical repair of a perforated jejunal ulcer with localized suppurative peritonitis was observed. There was suppurative inflammation of the anterior abdominal wall. Moderate coronary sclerosis was apparent, with partial thrombotic occlusion at the distal end of the left circumflex branch. The ulcer, located 1 cm distal to the stoma and on the opposite wall, measured 25 by 15 mm. The edges were sharply punched out and were thickened. In the lowermost portion, several linen sutures were present. A shallow defect, measuring 4 mm, occurred 3 cm below the anastomosis.

CASE 6—O S, a white man aged 45, had a gastrojejunostomy performed four years prior to entrance because of abdominal pain. For three years he was free of pain, but during the last year his trouble returned. He was advised to have surgical treatment, but he refused. Recurrence of pain four months before his terminal admission brought the patient to the hospital, but an attack of bronchitis prevented surgical intervention at that time. The terminal illness began four days prior to his admission with cramplike abdominal pain and persistent vomiting. Vomitus consisted first of gastric contents and later of yellowish brown feculent material. The patient had had no bowel movement for twenty-four hours prior to his entrance into the hospital, though flatus had been passed. On entrance he appeared to be in shock, with cold, clammy, cyanotic skin. The abdomen was distended, silent and moderately rigid. He died a few minutes after admission.

Clinical Diagnosis—The clinical diagnosis was intestinal obstruction due to postoperative adhesions.

Essential Anatomic Findings—Incarceration of the jejunum beneath an intra-abdominal band, recent peritonitis and a chronic peptic ulcer of the jejunum were observed. The ulcer, located on the posterior wall of the distal jejunal loop, measured 11 mm in diameter and was sharply punched out, presenting a dirty yellowish green floor.

CASE 7—H H, a white man aged 52, had a history of symptoms of ulcer of twenty years' duration. For four years prior to his gastrojejunostomy, performed fifteen years preceding his admission to the hospital, he had recurrent hematemesis and passed tarry stools. After the operation his symptoms disappeared until six weeks before admission, when he had a hemorrhage, from which he apparently recovered. However, seven hours prior to his entrance into the hospital he vomited a large amount of blood. The patient was in shock when admitted, with a blood pressure of 60 systolic and 30 diastolic, a respiratory rate of 32 per minute and imperceptible pulse. His hemoglobin concentration was 50 per cent, and the red cell count was 3,100,000 per cubic millimeter.

Clinical Diagnosis—The clinical diagnosis was bleeding peptic ulcer. The patient was given blood transfusions, but in spite of supportive treatment he died fifteen hours later.

Essential Anatomic Findings—Peptic ulcer of the posterior wall of the jejunum with erosion of an artery and massive hemorrhage was observed. The ulcer measured 15 by 10 mm and was located on the posterior wall of the afferent jejunal loop. The base of the ulcer was formed by the tail of the pancreas. An open blood vessel, 1 mm in diameter, was visible in the floor.

CASE 8—G. F., a white man aged 52, had symptoms of ulcer for three years prior to his entrance into the hospital, with epigastric pain. A diagnosis of duodenal ulcer was made, and a gastrojejunostomy was performed. At operation two ulcers were found. After the operation he was free of pain until one month prior to his terminal entrance, when pain became severe and was associated with nausea, loss of appetite, loss of 16 pounds (7.3 Kg.) in weight and passage of tarry stools. On entrance his pulse rate was 96 per minute, his respiratory rate 34 per minute and his blood pressure 120 systolic and 70 diastolic. There was tenderness in the epigastric region.

Clinical Diagnosis—The clinical diagnosis was marginal ulcer. About ten days after entrance the patient passed blood per rectum, and a proctoscopic examination was performed. No bleeding point was found. The abdominal pain became more severe, with extreme tenderness and diminished peristaltic sounds. Fluoroscopic examination revealed no free air in the peritoneal cavity. A flat plate showed dilatation of the large bowel suggestive of an obstruction of the colon near the suspected jejunal ulcer. The temperature rose to 101.6 F. on the eleventh day after entrance into the hospital, and the abdomen became rigid. Severe pain in the left lumbar region, accompanied by chills, was also noted. The clinical diagnosis of a left perinephritic abscess secondary to perforation of a jejunal ulcer was made. Operation was performed on the twelfth day after the patient's entrance into the hospital. The adhesions were broken up and a large amount of foul-smelling, clotted blood was drained from the wound, but no pus was found. The patient died three days after operation, fifteen days after his entrance into the hospital and six weeks after the onset of his acute symptoms.

Essential Anatomic Findings—A single jejunal ulcer with perforation and formation of a large abscess extending into the retroperitoneal tissues was observed in the left upper quadrant of the abdomen. Multiple perforations of the abscess into the descending colon and recent hemorrhages from the jejunal ulcer into the lumen of the intestine and the stomach had occurred. Recent perforation of a duodenal ulcer was observed, with sealing over by the right lobe of the liver. There was also a chronic peptic ulcer on the lesser curvature of the stomach. A laparotomy scar from gastrojejunostomy was visible, as was a recent surgical incision in the left lumbar region. On the greater curvature of the stomach there was a gastrojejunostomy stoma, measuring 20 mm in diameter. The mucous membrane was scarred and retracted, and on the left side of the stomach, at the line of opposition and continuing on the posterior wall of the jejunum, was an ulcer, 20 by 15 mm in size, with sharply punched-out margins. The ulcer, the base of which was formed by omentum, communicated by a small opening with a large abscess cavity at the splenic flexure of the colon. The abscess cavity communicated with the transverse colon and contained the upper pole of the left kidney, the left adrenal gland, the spleen and the tail of the pancreas. The cavity had been opened posteriorly by the recent surgical incision in the lumbar region. In the proximal portion of the duodenum, 15 mm from the pylorus, was a small (6 by 11 mm)

ulcer, the base of which was sealed by the liver. Immediately beneath the base of the ulcer was a small collection of purulent material, while at one point on its margin there was a small eroded, bleeding blood vessel.

COMMENT

These cases are briefly summarized in the accompanying table. It is interesting that in all 8 cases the patients were white men. The youngest was 40 and the oldest 60. The average age was 49. The

Summary of Clinical Data in Eight Cases

No	Age, Yr	Sex	Race	Lapse of Time Since Operation	Symptoms	Anatomic Cause of Death	Location of Jejunal Ulcer	Clinical Diagnosis
1	50	M	W	17 yr	Weakness, pallor, tarry stools	Hemorrhage, erosion of blood vessel	Two ulcers adjacent to stoma	Bleeding marginal ulcer
2	42	M	W	21 yr	Abdominal pains, vomiting	Perforation, peritonitis	Opposite stoma	Ruptured peptic ulcer with peritonitis
3	51	M	W	6 wk	Abdominal pains, bleeding	Perforation, peritonitis	9 cm below stoma in distal limb	Marginal ulcer with adhesions
4	60	M	W	9 yr	Bleeding, abdominal pains	Barbital poisoning, pneumonia	Opposite stoma	Barbital poisoning
5	40	M	W	11 yr	Abdominal pains, shock	Perforation, peritonitis	Opposite and 1 cm below stoma	Peptic ulcer with perforation
6	45	M	W	4 yr	Abdominal pains, vomiting, shock	Incarceration of loop of jejunum, peritonitis	Posterior wall of distal loop	Intestinal obstruction
7	52	M	W	15 yr	Bleeding, vomiting, shock	Erosion of blood vessel	Posterior wall of afferent loop	Bleeding peptic ulcer
8	52	M	W	3 yr	Abdominal pains, loss of weight, nausea	Perforation, abscess, erosion of blood vessel	Margin of stoma	Bleeding marginal ulcer
Aver, 49		8 (M)	8 (W)	Aver, 11 4 yr for 7 cases		Perforation, 4, erosion of blood vessel, 3		

interval following the surgical procedure varied from six weeks to twenty-one years. One of the patients had had no relief from symptoms following the gastroenterostomy, which was performed nine years prior to death. The interval between the operation and the recurrence of symptoms, except in the case just mentioned, was a matter of years. The interval between the recurrence of symptoms and the fatal complication was usually a few weeks, except in 2 cases. The cause of death was perforation with peritonitis in 3 cases, fatal hemorrhage in 2 cases, perforation followed by abscess formation in 1 case, intestinal obstruction in 1 case and barbiturate poisoning in 1 case.

The original operations included 6 posterior gastroenterostomies, 1 gastric resection and 1 exclusion operation in which the distal half of the stomach was made continuous with the duodenum and the proximal half was anastomosed to the jejunum

In 1 case there were two jejunal ulcers, in all the other cases the ulcers were single. Six patients had jejunal ulcers, and 2 had gastrojejunal ulcers. No healed ulcer scars were found in the stomach, while in the duodenum healed ulcer scars were seen in 2 cases. In 7 cases no active gastric or duodenal ulcers were present. In 1 case there were a duodenal and a gastric ulcer in addition to the gastrojejunal ulcer.

The indications for the original operation, according to the patients' histories, had been perforation (2 cases), hemorrhage (2 cases) and intractable pain (4 cases).

ETIOLOGIC FACTORS

Jejunal ulcer occurs most commonly between the ages of 40 and 50, and is much more prevalent in men than in women. A familial tendency has been suggested.

The cause of this type of ulcer is still obscure and will continue to be until the problem of peptic ulcer in general is solved. Probably the same factors influence the development of both types of ulcer. The vulnerability of the jejunal mucosa to the acid gastric contents is important. The presence of free acid, infection and vascular disturbances are the essential pathogenic agents. The activity of the last-named occurs soon after operation and is usually due to hemorrhage caused by puncture of a vessel with a needle or by damage to a blood vessel with a clamp. An area of decreased resistance is produced and may be followed by peptic digestion of the affected tissue. The collateral circulation is much better in the jejunum than in the proximal portion of the duodenum and the lesser curvature and the pyloric region of the stomach. However, as in other peptic ulcers, cardiac lesions with venous stasis, blood dyscrasias with petechiae and mucosal extravasation may predispose to erosion and subsequent ulcer formation. A large, small or poorly placed stoma with too short or too long an emptying time accompanied by hypersecretion is likely to cause ulceration. Nonabsorbable sutures have been found with no sign of active or healed ulceration. In 1 of our cases linen sutures were found in the base of the ulcer.

Other theories of causation include von Bergman's theory of vascular spasm, Konjetzney's theory of local infection and the constitutional theory. A large amount of hydrochloric acid and of pepsin in the gastric contents no doubt is important and is the active cause of the erosion or digestion of the mucosa and the jejunal wall.

PATHOLOGIC FACTORS

Jejunal ulcer usually occurs within 2 cm of the stoma, in the efferent limb of the jejunal loop, and sometimes directly opposite the stoma. The afferent limb is protected by the alkaline duodenal contents.

A marginal, or gastrojejunal, ulcer always involves the stoma and is usually found on one side of it, often stopping precisely at the junction. Here we must differentiate immediate postoperative sloughing and ulceration. Sloughs are probably due to interference with the mucosal circulation. They usually heal, although acute ulceration with transition to chronic ulceration may occur.

A jejunal ulcer may be acute, subacute or chronic. Grossly and microscopically, it is similar to peptic ulcer. However, acute and subacute forms of true jejunal ulcer are prone to cause serious complications. A jejunal ulcer is round or oval or if bounded by the anastomotic junction is irregular in shape.

The course of development of a jejunal ulcer is similar to that of other ulcers. Healing, erosion of blood vessels with hemorrhage, perforation followed by peritonitis or abscess formation, adhesions, gastrocolic fistula and stenosis of the stoma occur. The jejunum is thin walled and unsupported. Branches of the mesenteric vessels reach the mesenteric border and pass circularly about the jejunum. Ulcers opposite the stoma or on the lateral walls often overlie the larger branches. Thus, the jejunal ulcer carries the same hazard of perforation as does the duodenal ulcer in the anterior wall. In addition, the danger of erosion of blood vessels, the largest of which lie opposite the stoma, is as great as in cases of duodenal ulcers situated on the posterior wall. Perforation may occur into the peritoneal cavity, into a walled-off area or into the colon, with subsequent development of peritonitis, formation of an abscess or formation of gastrocolic fistula, respectively. Jejunal ulcer is prone to cause symptoms early, while gastrojejunal ulcer tends to become chronic and persist over a long period, occasionally causing obstruction.

This tendency to chronicity and relative freedom from fatal complications is no doubt the reason that we found only 2 cases of gastrojejunal, or marginal, ulcers in our series.

In a review of the literature, it is clear that there has been a tendency to blame the operative procedure for anastomotic ulcer. After modification of the surgical procedure it was found that the ulcer still developed. The anterior gastroenterostomy was succeeded by the posterior short loop gastroenterostomy, which in turn was modified by various enteroanastomoses, such as the "en-y" operation. Then subtotal gastric resection, with or without gastroenterostomy, was hailed as the only means

of preventing the development of jejunal ulcer. Now it is contended by many surgeons that two thirds to three fourths of the stomach must be resected to prevent this complication.

SUMMARY

The history of the knowledge of anastomotic ulcer and the evolution of present day opinion regarding development of such an ulcer are discussed.

Necropsy findings in 8 cases of anastomotic jejunal ulcer occurring after gastrojejunostomy alone or combined with gastric resection are reported. In all the cases the patients were white men and the average age was 49. The apparent rarity of this condition in a series of 13,000 postmortem examinations is noted. Perforation and fatal hemorrhage were frequent causes of death. The lapse of time from surgical intervention for the original peptic ulcer to the fatal termination varied from six weeks to twenty-one years. The average for 7 cases was eleven and four-tenths years.

PATHOGENESIS AND PATHOLOGIC CHANGES IN PEPTIC ULCER, AND PRODUCTION OF PAIN

JACOB RABINOVITCH, M D

BERNARD PINES, M D

AND

IRA TEICHER, M D

BROOKLYN

Various ideas have been propounded from time to time to account for the development of gastroduodenal ulceration, but the underlying agent or agents are still undetermined. It is true that under certain conditions peptic ulcer will develop in the human being or that ulcers may be produced experimentally in animals, but either occurrence throws little light on the real problem of the condition. The peculiar and almost constant localization of the lesion in the lesser curvature just proximal to the pylorus has been given special etiologic significance, and it has been often correlated with an assumed special exposure of this part of the stomach to irritation resulting from the strongly acid chyme.

A review of the literature reveals a wide discussion in reference to the pathologic anatomy and symptomatology of peptic ulcer. The symptom most commonly encountered in this lesion consists of pain, invariably described as burning (heart burn) in character. The pain usually appears within a definite period after the intake of food and is referred to the upper part of the abdomen. It has also been shown that there exists a definite parallelism between the occurrence of this symptom and the anatomic changes in the wall of the ulcerated stomach and duodenum, so much so that one expects to find definite pathologic changes in these organs whenever this syndrome of pain is encountered.

Because of the difficulties in drawing conclusions from the confusing and contradictory experimental results obtained by different observers, we have undertaken the present study in order to furnish additional information concerning the pathogenesis of peptic ulcer. An analysis of the various cases has also yielded adequate proof as to the probable cause of the pain in peptic ulcer, and this will be discussed in some detail later.

The present study deals with a group of some 200 patients in whom pain was the outstanding symptom. The patients for the most part had definite peptic ulcers, and because of the obvious relationship of the

pain to the visceral nervous mechanism of the stomach and duodenum, it seemed desirable to study the different pathologic changes which occur in cases of peptic ulcer with special emphasis on the changes about the nerve fibers and nerve endings. Sections were routinely taken through the ulcerated area of the stomach or duodenum and were stained with hematoxylin and eosin and on occasions with Van Gieson's or Mallory's stain. The blocks were cut at random with no attempt to place the sections in the region of the nerves.

It is also the purpose to discuss and describe as impartially as possible the various theories which have been advanced to explain the etiology and pathogenesis of peptic ulcer. An attempt will be made to limit this discussion to those facts and theories which appear to have the most specific basis, rather than to review the opinions expressed by many different authors. To do this intelligently and clearly it is necessary to have an accurate understanding of the anatomy and physiology of the parts involved, so those phases will be briefly reviewed.

The secretory cells of the mucosal glands of the stomach are essentially of two types, namely, chief, or pepsin-secreting, cells and parietal, or acid-producing, cells. These glands are particularly numerous in the fundus and along the lesser curvature of the stomach, the latter region has been frequently referred to as the *Magenstrasse*, or stomach path. In the pyloric portion the cells are largely mucus producing and yield a secretion which is definitely alkaline in reaction. The muscular coat is described as consisting of three layers, an inner (oblique), a middle (circular) and an outer (longitudinal). The nerves to the stomach are derived from the vagus nerve and from the celiac ganglions of the sympathetic nervous system. The vagal fibers unite with the sympathetic fibers from the celiac plexus, which pass to the stomach with the branches of the celiac artery. The nerve fibers, which are chiefly nonmedullated, form two gangliated plexuses, the myenteric plexus of Meissner and the submucous plexus of Auerbach, in the muscular and submucous coats respectively (figs 1 and 2). The results of numerous experiments seem to show conclusively that in general the fibers along the vagal path are motor, while the fibers coming through the sympathetic system are mainly inhibitory. It has also been generally accepted that pain sensations arising in the stomach are propagated along the sympathetic fibers (Kuntz, Moore).

Considerable importance has been attached to the frequent occurrence of hyperacidity in patients with peptic ulcer, and it has been assumed that hyperacidity is of primary importance in the genesis of these ulcers. Also, different methods of experimental approach have been used to explain the development of peptic ulcer but some of these are suitable only for animal experimentation. Thus, the effect of hyper-

acidity experimentally produced by the feeding of dilute hydrochloric acid and other acids has been studied. Whereas such an artificial hyperacidity may produce lesions ranging from simple erosions to actual ulcerations, the conclusion reached by most observers is that it is of no significance except when the acid is administered in huge doses, far in

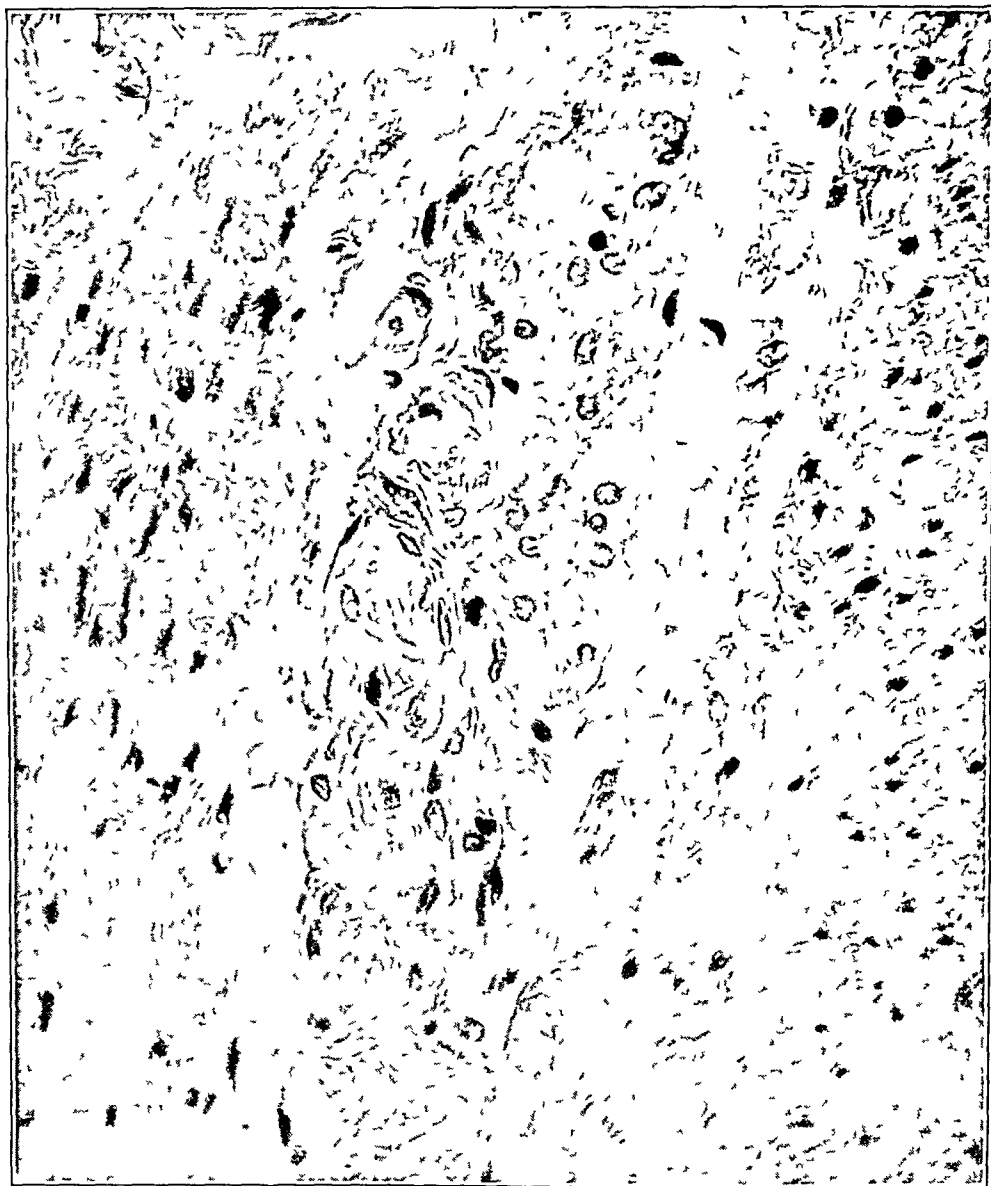


Fig 1—Ganglion cells and nerve trunk in the muscular coat of the normal stomach

excess of the physiologic needs of the experimental animal. Langenskiöld¹ and Mann and Bollman² have shown that in dogs with gastric

1 Langenskiöld, F. *Skandinav Arch f Physiol* **31** 1, 1914

2 Mann, F. C., and Bollman, J. L. *Experimentally Produced Peptic Ulcers Development and Treatment*, *J A M A* **99** 1576 (Nov 5) 1932

fistulas in whom unbuffered dilute hydrochloric acid was allowed to trickle through the stomach and duodenum there developed a gradual exhaustion in the defensive powers of the mucosa, this resulted first in distress and later in pain, with reddening, irritation and finally superficial ulceration. Mann³ attached much importance to the injurious

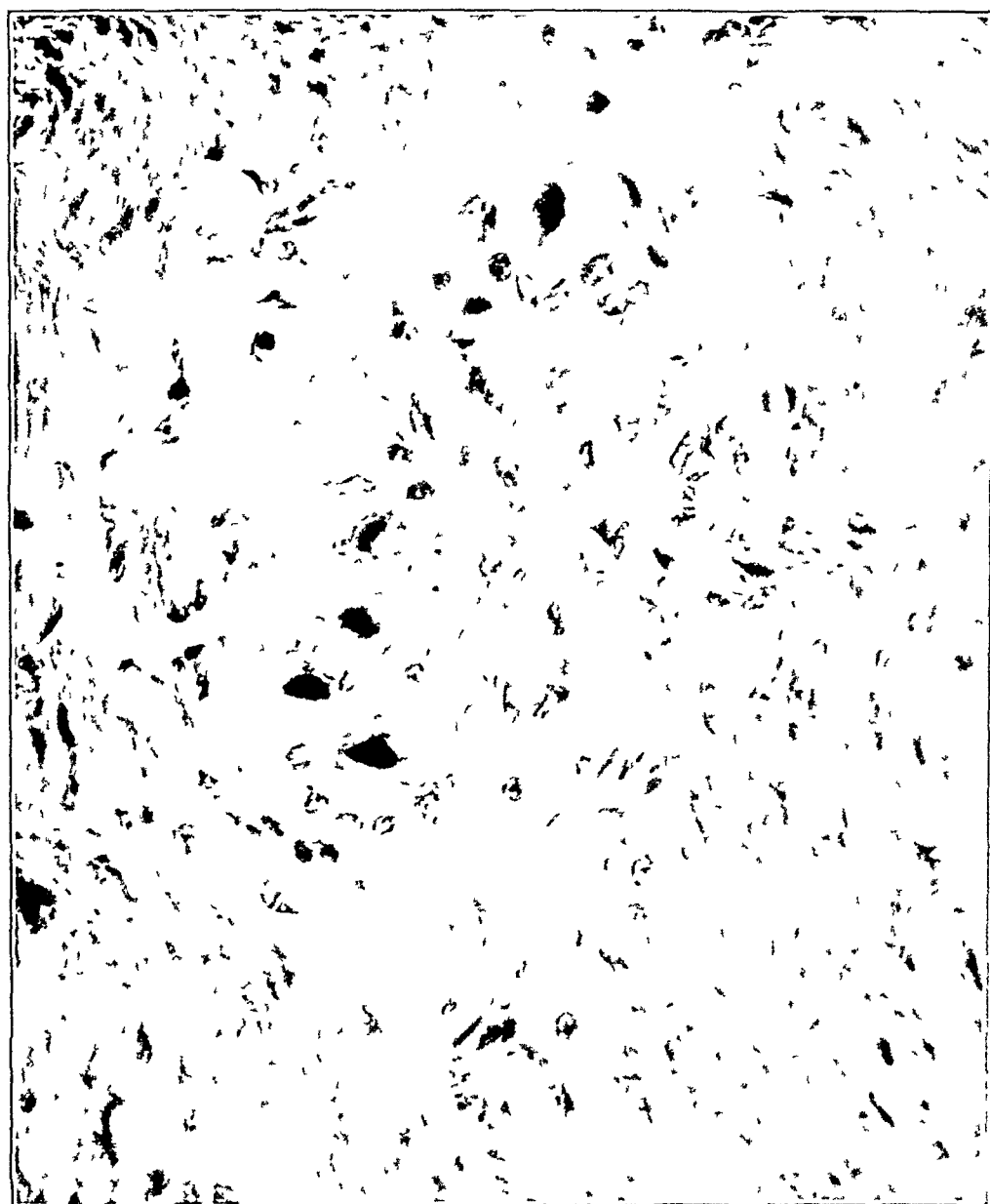


Fig 2—High magnification of ganglion cells in the musculature of the normal duodenum

and destructive effects which the acid chyme has on gastric mucosa not protected by the mechanism for diluting, buffering and neutralizing the acidity of the gastric contents. According to him these ulcers never occur in a mucosa which is not exposed to acid gastric juice. Schmidt

3 Mann, F. C. Brit. M. J. 1: 707, 1939

and Fogelson⁴ have shown, on the other hand, that acid gastric juice of itself is not sufficiently destructive to overcome the normal protective factors which inhibit or prevent gastroduodenal ulceration. Their findings are somewhat at variance with those of Mann, by sham-feeding esophagostomized dogs and thereby inducing an increased flow of acid



Fig 3—Gastric ulcer, with deep crater and fibrosed wall beneath it

gastric juice, they were unable to produce in these animals any gastric or duodenal ulceration. DeBakey⁵ and Ochsner⁶ expressed the opinion that at least two factors operate in the production of a peptic ulcer

4 Schmidt, C R., and Fogelson, S J. *Am J Physiol* **120** 87, 1939

5 DeBakey, M. *Surgery* **2** 653, 1937

6 Ochsner, A. *Surgery* **2** 786, 1937

One is a predisposing factor, usually of a chemical, mechanical or infectious nature, the other is a precipitating factor caused by constitutional or tissue susceptibility to ulceration. These authors have expressed the belief that erosions of the stomach may occur in the gastric mucosa injured by either excessive acidity, irritating foods or infecting micro-



Fig 4—Inflammatory process in peptic ulcer showing diffuse infiltration of round cells, edema and thrombosed vessels

organisms, the erosions may turn later into chronic indolent ulcers in certain susceptible persons with an ulcer diathesis. Other observers have stressed some derangement of the nervous system as the most significant single factor in the causation of peptic ulcer. It has been assumed that the constant, irritating nervous stimuli eventually lead to

localized spastic contracture of the gastroduodenal musculature, which in turn effects areas of mucosal and submucosal ischemia and ulcer formation

At the present time it cannot be definitely stated what underlying abnormality is responsible for the predisposition to ulceration. Animal



Fig 5—Peptic ulcer, showing marked endothelial proliferation and considerable narrowing of the lumen of the vessels

experimentation, although of importance, does not necessarily always apply to changes in the human economy, and consequently experimental efforts should be directed toward human criteria whenever possible. The present state of knowledge permits only theorization regarding the practical application of this experimental work to man. There is no

doubt that more than one factor is concerned in the production of peptic ulcer in different persons. There come to mind at least three possible explanations for the cause of this disease, namely, (1) hyperacidity and tissue susceptibility as suggested by DeBakey and Ochsner, (2) sympathoadrenal hyperinnitability as suggested by Crile or (3) vagotonia as suggested by Beigmann.

A histopathologic study of this group of patients with peptic ulcer revealed several significant facts. Section through the ulcer showed the typical changes of a chronic gastric ulcer, with a fibrous floor covered with granulation tissue, surrounded by a layer of necrotic tissue (fig. 3). The inflammatory process was diffuse and extended far beyond the area of ulceration, it generally involved all the coats of the stomach and duodenum and reached as far as the serosa. The inflammatory reaction was of a chronic nature and consisted of a cellular exudate composed mainly of monocytes and to a less extent of polymorphonuclear neutrophils, eosinophils and plasma cells. The fibrous reaction was equally striking and showed an abundance of fibroblastic proliferation replacing the normal structures of the gastric or duodenal wall (fig. 4). The vascular changes were confined in the main to the smaller arterioles which showed marked mural thickening with a corresponding diminution in the caliber of the lumen. The increased thickness of the vessel wall was primarily due to endothelial proliferation, the latter forming several intraluminal, concentric layers of cells which almost completely obliterated the lumen (fig. 5). Occasionally, too, the lumen of the affected vessel was partly or completely occluded by thrombus formation. Obviously, the reduction in the caliber of the sclerosed or thrombosed blood vessel caused considerable interference with the flow of blood, and hence also, with the nutrition of the stomach and duodenum. The ischemia which is apt to follow such vascular changes may be responsible, in part at least, for the ulcer formation.

The histopathologic changes about the nerve structures were similar in all of the 200 patients studied, and may be briefly discussed as follows. An inflammatory exudate was seen to surround many of the smaller and larger nerve trunks and their terminals, lying within the depth of the ulcerated wall. Often, too, the nerve fibers became coiled up like little nodules and bore a striking resemblance to the neuromas commonly seen in stumps (fig. 6). The perineuritic inflammatory changes were quite extensive at times and consisted largely of dense fibroblastic proliferation and round cell infiltration. Nerve fibers as well as ganglions were often enclosed within areas of inflammation, the latter consisting for the most part of dense aggregates of small and large round cells. These changes were widespread, so that in all parts of the ulcer the appearances under the microscope were similar.

It may be of interest in this connection to cite a few of the cases which were observed in this hospital, with the purpose of showing the relationship which exists between the clinical symptoms and the inflammatory changes around the nerve elements. Most of our material was

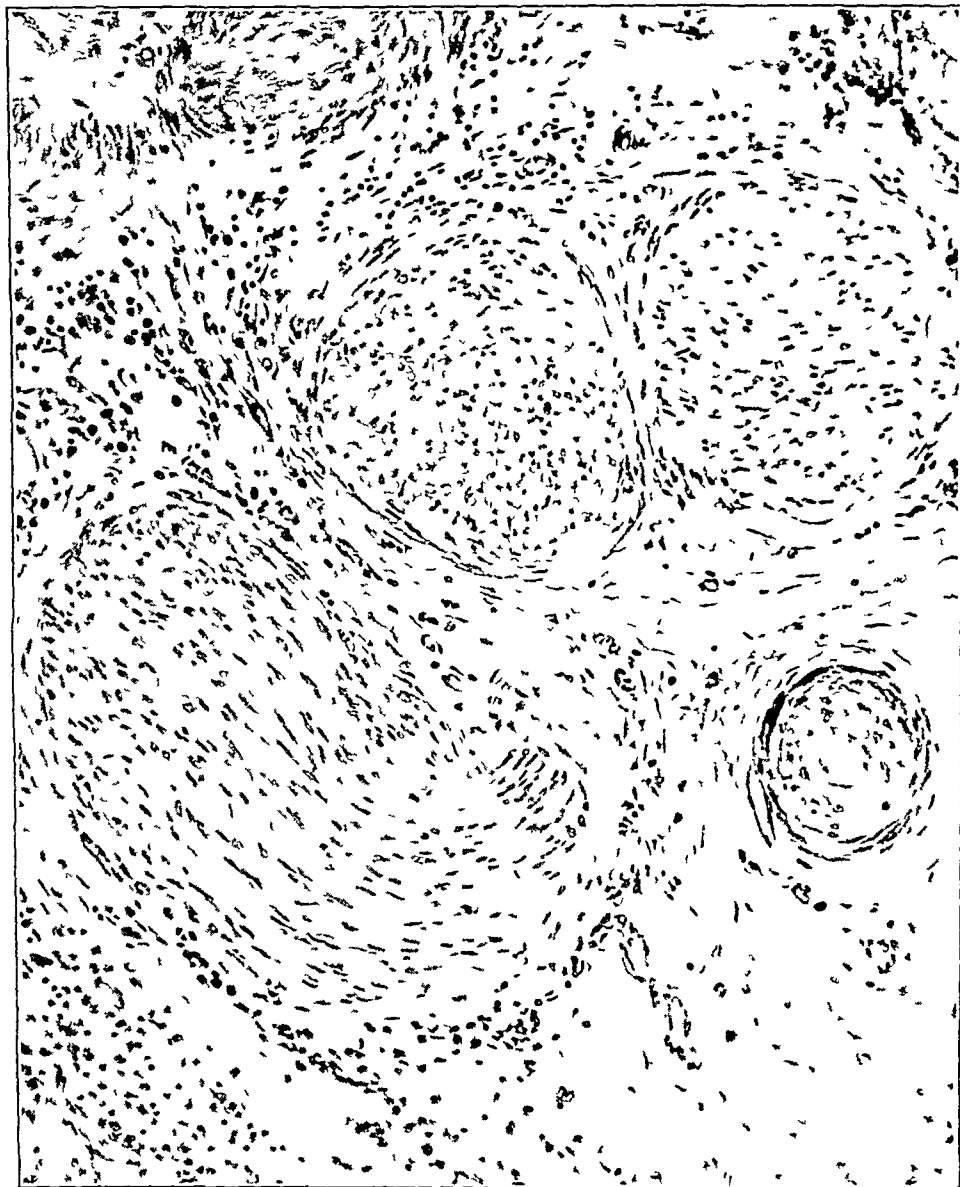


Fig 6—Large nerve trunks surrounded by an inflammatory exudate consisting of round cells and fibrous tissue

received in the form of a portion of the stomach, including the ulcer-bearing area, removed by partial gastrectomy

CASE 1—The patient was a 32 year old man who complained of pain in the epigastrium of one year's duration. The pain occurred half an hour after meals and was relieved by foods and alkalis. Occasionally the pain persisted all day and sometimes it awoke the patient at night. There had been some remissions from

pain The appetite was fair, but the patient was afraid to eat because pain followed No nausea or vomiting occurred The bowels were normal, there was no melenæ The past and the family history revealed no relevant data A diagnosis of ulcer of the stomach was made, and a partial gastrectomy was performed, including the ulcer-bearing portion

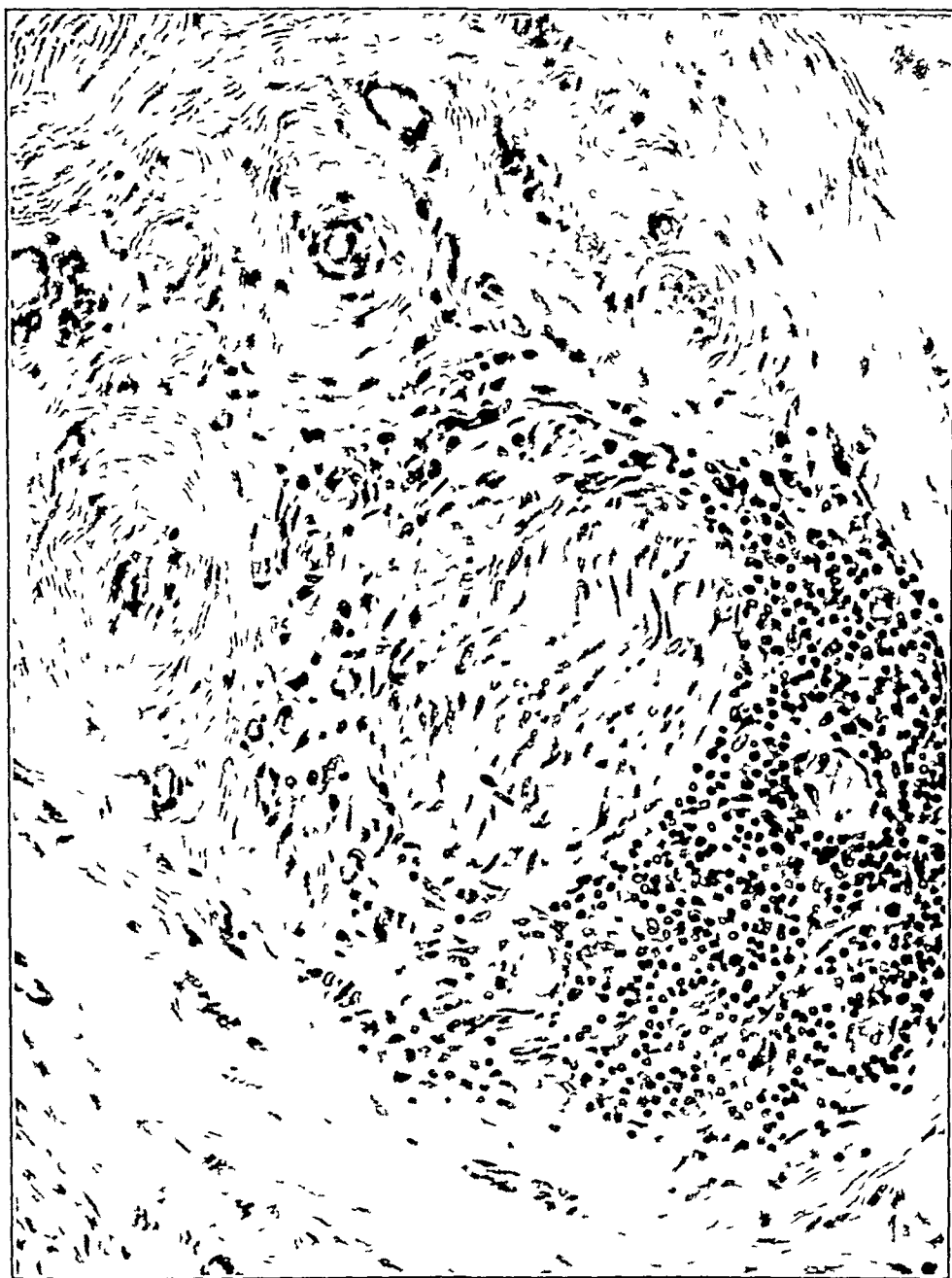


Fig 7—Nerve fibers surrounded by a dense area marked by the infiltration of round cells and the overgrowth of fibrous tissue

When the stomach was opened, the ulcer, found on the lesser curvature, had all the appearances of a simple chronic gastric ulcer with slightly thickened edges and a fairly deep crater Histologic examination of the specimen revealed a diffuse inflammatory process involving practically the entire thickness of the gastric wall The changes around the nerve fibers were striking Figure 7 shows one such

area where a nerve fiber is surrounded by a dense collection of round cells and overgrowth of fibrous tissue. The adjoining blood vessels show marked thickening of the wall and narrowing of the lumen.

CASE 2—A 44 year old man entered the hospital because of abdominal pain, nausea and vomiting. For six years prior to admission he had episodes of pain in the upper part of the abdomen coming approximately within an hour after

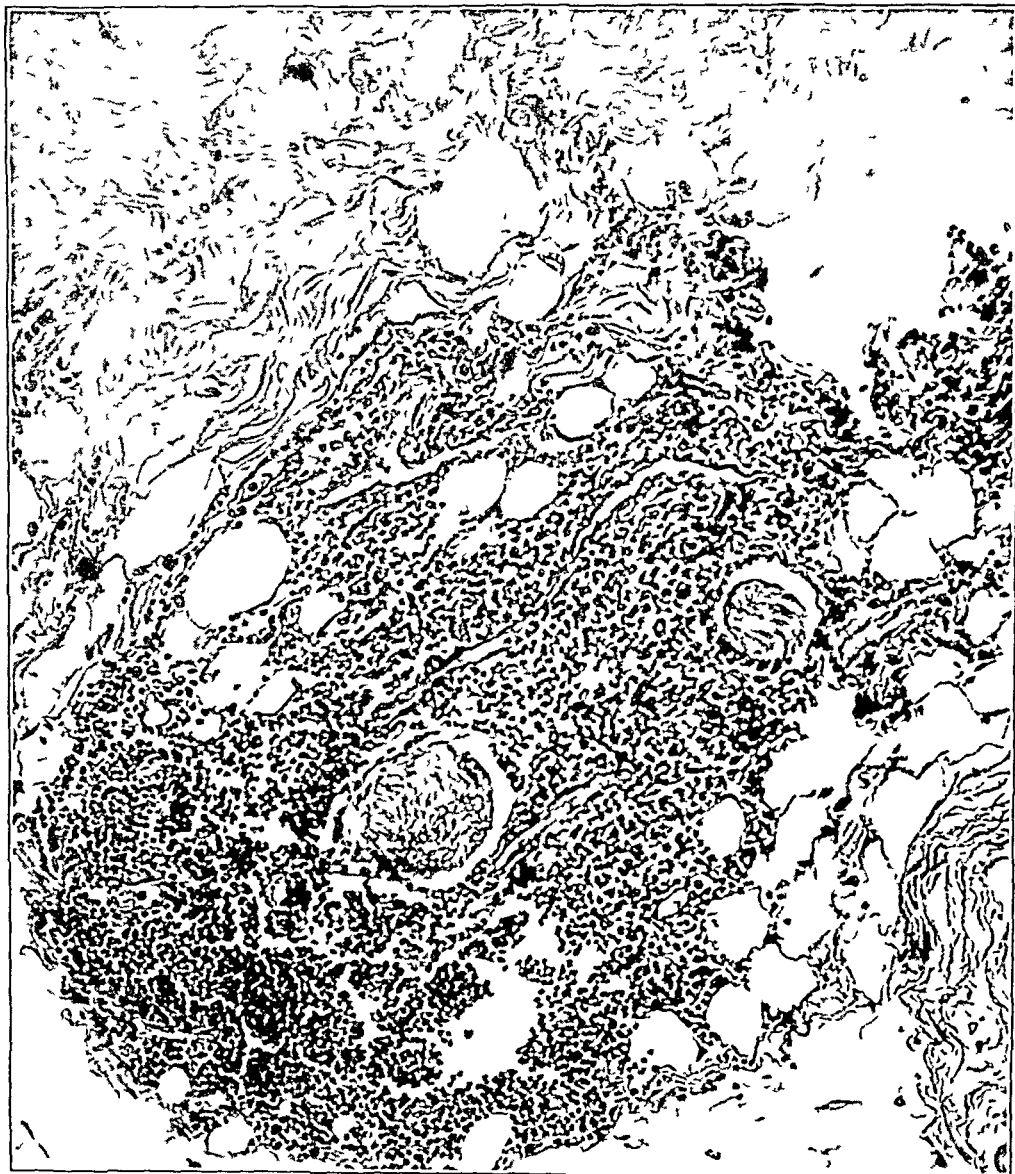


Fig 8—Dense aggregates of round cells and fibrous tissue enclosing nerve trunks in the wall of the ulcerated stomach

meals. The pains were largely relieved by alkalis. He was also subject to attacks of dizziness which sometimes resulted in fainting spells. A diagnosis of peptic ulcer was made, and a partial gastrectomy was performed.

Pathologic examination of the specimen showed ulceration of the mucosa extending as far as the muscularis. Many of the nerve fibers were surrounded by zones of inflammation, the latter consisting for the most part of round cells and dense fibrous tissue (fig 8).

CASE 3—The patient, a man aged 39, was admitted to the hospital because of severe hematemesis. For several years prior to his admission he was subject to attacks of heart burn appearing about two hours after meals and relieved by sodium bicarbonate. A diagnosis of bleeding duodenal ulcer was made, and he was operated on for that condition. The patient died several days after the operation,

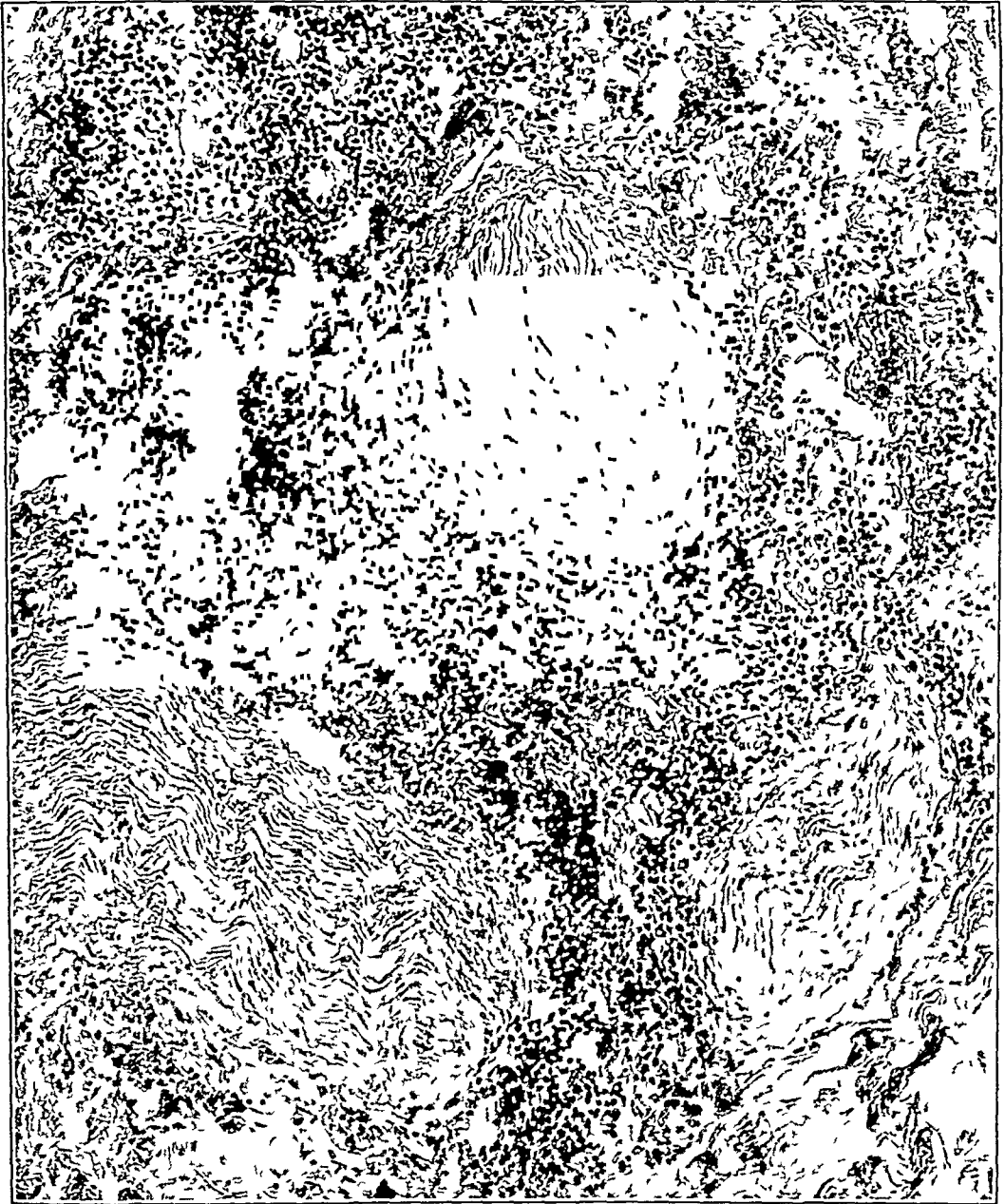


Fig 9—Nerve trunks surrounded by a localized zone of round cells and diffuse fibrosis in a duodenal ulcer

and at necropsy a large duodenal ulcer was found. Histologic examination of the ulcerated duodenum revealed a diffuse inflammatory process particularly in the region of the various nerve fibers, as shown in figure 9.

CASE 4—A 42 year old man was admitted for epigastric distress coming shortly after the taking of food. He dated the onset of his illness fifteen years prior to his present admission. Recently the pains were more frequent although they were relieved at times by alkalis. A diagnosis of peptic ulcer was made, and

at operation a large ulcer was found near the pyloric end of the stomach, a partial gastrectomy was performed. Microscopic examination of the specimen showed in addition to the ulcerated gastric mucosa a diffuse inflammatory cell reaction and fibroblastic proliferation. Some of the nerve fibers and ganglions were enclosed in a bed of dense fibrous tissue scattered in which were numerous round cells (fig 10)

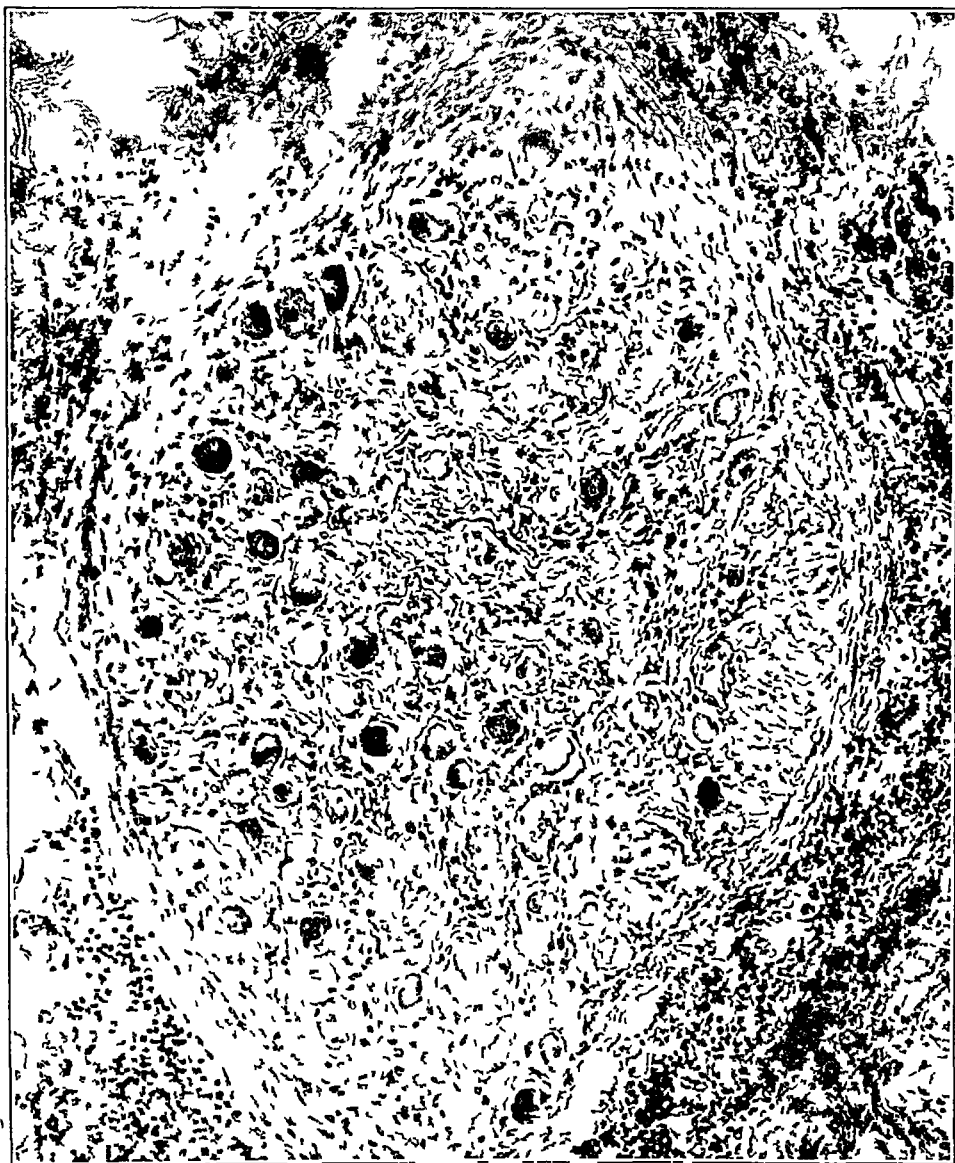


Fig 10—Large ganglion in the musculature of a gastric ulcer. There is a moderate number of round cells and a considerable amount of fibrosis surrounding the ganglion.

In summary, the findings in this whole group of patients revealed that the lesions of all of them had a closely related pathologic structure. The histologic features of the lesions may be briefly summarized thus: (1) abundant infiltration with round cells and to a less extent also with polymorphonuclear neutrophils, eosinophils and plasma cells, (2) pro-

found changes in the blood vessels, (3) widespread new formation of fibrous connective tissue, (4) inflammatory changes about the nerve fibers and ganglions

In the light of the foregoing pathologic observations one may correlate the histologic changes with the production of pain and perhaps also with the pathogenesis of peptic ulcer. The various histopathologic observations made in these cases appear to shed some light on the relationship existing between the inflammatory changes about the nerve fibers and ganglion cells, as well as on the problem of the development of peptic ulcer. Histologic studies of the ulcers also justify the belief that there is a continuous interplay among the nervous, vascular and muscular elements of the stomach and duodenum which is responsible for the creation and maintenance of chronicity of peptic ulcer. The enclosure of many of the nerve elements within zones of inflammation leads to constant irritation of these nerves, this, in turn, may produce vasospasm, muscle spasm, ischemia, necrosis and ulceration. One of the most interesting facts disclosed in the experimental studies of recent years is the observation made by Telford and Stopford, who showed that the feeding of ergot to Leghorn cockerels for a period of several weeks resulted in continuous spasm of the arteries to the combs. This was followed by proliferative endarteritis of the walls and thrombosis of the vessels. They believed that similar changes might occur in the arteries of the arm following continued irritation of the sympathetic nerves, with the production of vascular changes and gangrene of the fingers. On the basis of these experiments and the previously described pathologic observations, we are inclined to believe that the proliferative endarteritis noted in the ulcerated stomach and duodenum may be traced directly to irritation of the sympathetic nerve fibers by the existing inflammatory reaction. The fact disclosed in these studies is that nerve fibers, both sympathetic and vagal, lying within the ulcerated gastric and duodenal wall are subject to constant irritation because of the surrounding fibrosis and inflammatory cellular exudate. Sympathetic nerve fibers in the wall of the stomach and duodenum, therefore, are irritated by the surrounding chronic fibrosis, and this may lead to such vascular changes as vasospasm and proliferative endarteritis. There is no doubt also that the manition to the tissues caused by the retarded flow of blood through the partly or completely obliterated vessels results first in necrosis and later in ulcer formation.

It may be said, then, that endarteritis, vasospasm and spastic contraction of the musculature may be produced in the stomach and duodenum as a result of irritation of the nerves caused by inflammation. The ischemia which is apt to follow such changes may be responsible, in part at least, for the necrosis and ulceration of the gastroduodenal wall.

The question remains, however, as to what initiates the inflammatory process which later in its course produces nerve irritation, ischemia and necrosis. One of the most valuable explanations concerning the fundamental cause of peptic ulcer lies in the fact that early in its development the ulcer begins as a localized area of gastritis, this is caused as a result of the action of one or several agents, of which hyperacidity perhaps heads the list. This last hypothesis is corroborated clinically, since many of the patients with peptic ulcer show initial clinical evidence of increased acid secretion, it is also supported experimentally, as shown by the work of Mann and others. There is no doubt also that trauma consequent to the intake of rough, irritating foods, particularly in the presence of an increased acid concentration, will suffice in certain susceptible persons to produce a local erosion and an inflammatory reaction. On this basis one would place the primary etiology of the disease in whatever causes an initial gastritis or erosion of the gastric mucosa, which later in its course leads to focal nerve irritation, endarteritis, vasospasm, muscle spasm, ischemia and necrosis. While this phase of the problem is based too much on speculation to warrant its present application to the wide fields of gastroduodenal ulceration, nevertheless it would appear to bear definitely on a large number of cases within that field.

A review of the literature on the physiology and anatomy of visceral pain as it applies to gastric pain reveals many controversial points, and in this presentation no attempt will be made to give any detailed bibliography. Two main theories have been offered to account for the cause of pain in peptic ulcer: one that the pain is due to deep muscle contractions and the other that it is due to an increase in the acidity of the fluids bathing the ulcer. According to Alvarez⁷ the main factor concerned in the production of ulcer distress is a sensitization of nerve endings in the upper part of the digestive tract which causes them to respond painfully either to the presence of acids or to certain types of contractions in the stomach, duodenum or esophagus.

Sufficient data have been accumulated from a study of the foregoing material to permit the conclusion that the pain in peptic ulcer is due primarily to a perineuritis and only secondarily perhaps to such factors as hyperacidity and contraction of the gastric musculature. It is conceded that painful stimuli in a sensory nerve fiber may develop either as a result of local ischemia or stretching of the nerve fiber. Both these factors are found to exist in the case of peptic ulcer. The ischemia is effected through occlusion of the vascular channels and the inflammatory edema in the region of the ulcer while the stretching of the nerve fibers

⁷ Alvarez, W. C. *The Mechanism of the Digestive Tract*, New York, Paul B. Hoeber, 1928.

is brought about by the diffuse fibrosis which encircles the nerve fibers. Womack⁸ has shown that the same forces operate in the causation of pain in disease of the gallbladder. It is also conceivable that irritation of the nerve fibers may lead to ischemia because of spastic contraction of the gastroduodenal musculature and that this in turn will produce pain. The factor of ischemia as a cause of pain has long been recognized. The agonizing pain which is experienced when the coronary arteries are occluded is well known as are the pains produced in the extremities when the blood supply is interrupted. The pathologic changes noted about the nerves in the ulcerated stomach and duodenum are such that they would tend to increase the tension on the nerves and to decrease the blood supply. Such factors as stretching and ischemia must be considered as important pain-producing agents whenever there are marked fibrosis, edema and diminished circulation around the nerve fibers.

Experiments conducted by Moore⁹ have shown conclusively that the potassium ion is markedly irritating to both pain endings and pain fibers even when used in isotonic solutions. In inflammation the potassium ion is poured out into the intercellular fluids which bathe the nerve endings, and Habler and Hummel¹⁰ have reported large concentrations of potassium in inflammatory exudates, capable of stimulating pain elements. It seems, then, that another cause of pain in peptic ulcer may be the potassium ion in the inflammatory exudate which irritates the pain nerve fibers.

In a general way it may be said, then, that a number of factors are responsible for the cause of pain in peptic ulcer. These may be briefly summarized as follows:

- 1 Ischemia produced as a result of vascular occlusion and contraction of the gastroduodenal musculature. In ischemic lesions there is a tendency for accumulation of acid radicals which are known to irritate nerve endings.

- 2 Inflammatory exudate as a source of visceral pain is obvious. The interstitial tension developed in many inflammatory swellings may act to compress and distort pain endings to the point of stimulation. Furthermore, pain endings are highly sensitive to the potassium ion, and the latter is found in increased amounts in inflammatory exudates.

To what extent the increased gastric acidity plays a part in the causation of pain is open to question. On the clinical evidence it is plain that while hyperacidity may be a cause or a contributory factor, it cannot be the sole direct cause. It is feasible that an increased gastric acidity

8 Womack, N. A. *Surgery* 4:847, 1938.

9 Moore, R. M. *Surgery* 3:534, 1938.

10 Habler, C., and Hummel, R. *Klin. Wchnschr.* 7:2151, 1928.

may effect painful sensations through irritation of the exposed nerve fibers in the ulcerated wall and through spastic contractions of the smooth muscle fibers of the stomach and duodenum

SUMMARY AND CONCLUSIONS

Studies of peptic ulcer have been diligently pursued on laboratory animals and on human beings by many investigators. Although laboratory results have advanced information concerning this subject considerably, such findings do not satisfactorily and entirely explain conditions in human beings, for there exists much variation in the physiologic behavior of laboratory animals as compared with human beings.

Evidence is adduced from the literature emphasizing the fact that several factors are concerned in the genesis of gastroduodenal ulceration.

On the basis of this present study, focal gastritis and erosions are most closely associated with the primary etiology. Chronicity of the indolent ulcer, on the other hand, is dependent on changes in the vascular, muscular and nerve elements of the gastroduodenal wall.

The pain in peptic ulcer is due primarily to local perineuritis, which is a common occurrence in peptic ulcer. Ischemia and inflammatory exudates are other contributory factors.

THE ELECTROCARDIOGRAM IN LATER LIFE

MAURICE ELIASER JR., M D

AND

BENJAMIN O KONDO, M D

SAN FRANCISCO

The increasing number of persons who are attaining the age of 70 and the frequency with which they suffer attacks of acute coronary occlusion make it expedient that certain standards of normalcy be established electrocardiographically for this age group. The series of records presented here was assembled in an attempt to determine what constitutes a normal electrocardiogram for an elderly person without symptoms of cardiovascular disease.

MATERIAL

One hundred persons over 70 years of age were selected for this study. Accurate and painstaking histories were obtained in order to eliminate any one who had manifestations of impaired cardiac function other than that which could be properly ascribed to aging alone. All persons without physical signs of cardiovascular disease except mild hypertension (pressure not exceeding 150 mm of mercury systolic and 90 mm diastolic) and moderate ventricular enlargement with an apical impulse palpable less than 12 cm to the left of the midsternal line, were included. However, persons with abnormally decreased vital capacities, diastolic murmurs or unusually increased basal cardiac dullness were excluded. Furthermore, basal pulmonary rales, hepatic engorgement, increased venous pressure, dependent edema, gallop rhythm and pulsus alternans were considered indications for exclusion from this series. Systolic, mitral and/or aortic murmurs of uncomplicated arteriosclerotic origin have been observed to be associated with the normal process of aging¹ and were therefore not excluded if uncomplicated by other pathologic conditions. Associated disorders, such as benign prostatic hypertrophy, ocular diseases, hypacusis, peptic ulcer and diverticulosis coli, were encountered in 15 per cent of the persons, however, they were not believed to be of clinical significance in producing alterations in the cardiovascular system.

Selections were made from a group of ambulatory persons residing in an institution for the care of the aged. None was or had been hospitalized for a period of at least six months prior to the examination. The few who had been bed patients had been under treatment for conditions not referable to the cardiovascular system. Fifty-six per cent of the men and 37.5 per cent of the women of this series were gainfully employed in various occupations at the institution, working in the wards, waiting on tables, gardening, cooking, weaving or sewing. The remainder had

From the Department of Medicine, University of California Medical School, and the Laguna Honda Home Infirmary, Department of Public Health.

1 Cohn, A. E., in Cowdry, E. V. Problems of Ageing, Baltimore, Williams & Wilkins Company, 1939, p. 133.

been similarly employed within the past year but, although they were able to work, had been unable to find employment because of the limited number of positions available

The distribution of the persons selected for this study as to age is compiled in table 1. It will be noted that no person under the age of 70 was included and that the greatest age was 92 (table 1)

The data obtained in this study resulted from observations made on the standard three lead electrocardiogram and a lead IV which is IV F of the Committee on Precordial Leads of the American Heart Association²

RESULTS

The electrocardiographic findings for the 100 records obtained are listed in table 2. The various pathologic recordings are given individually and will be discussed separately under the headings noted in the table (table 2)

TABLE 1—*Distribution of Age and Employability of Persons over 70 Years of Age Without Significant Cardiovascular Disease*

Age	Men	Women	Total
70-75	37	5	42
76-80	15	17	32
81-85	9	9	18
Over 85	7	1	8
Total	68	32	100
Gainfully employed	38 (56%)	12 (37.5%)	50
Unemployed	26	20	46
Intermittently employed	4	0	4
Total	68	32	100

Axis Deviation—In 62 persons, left axis deviation was found, none presented right axis deviation. Two persons with right axis deviation were encountered during the selection of this series but were eliminated because the first one had a deformity of the chest, being an achondroplastic dwarf, and the second had dyspnea on exertion which probably was the result of long-standing bronchial asthma. The absence of any other acceptable instances of right axis deviation would seem to warrant the conclusion that the cardiographic finding of an electrical axis to the right in an elderly person in the absence of pulmonary disease suggests cardiac disease. It is one of the most significant findings⁴ when encountered.

Voltage of the Major Deflections—Under the subheading "Abnormally low voltage" are included the persons with electrocardiograms

2 Standardization of Precordial Leads. Supplementary Report, Am Heart J 15 235, 1938

3 Footnote deleted

4 Comeau, W. J., and White, P. D. The Clinical Significance of Right Axis Deviation in the Electrocardiogram, Am Heart J 18 334, 1939. Ehler, M., Jr., and Kongsberg, J. Electrocardiographic Findings in Cases of Ventricular Aneurysm, Arch Int Med 64 493 (Sept) 1939

presenting major deflections under 5 mm in height (fig 1) Each lead was separately calibrated and the calibration recorded on the film so that an electromotive force of 1 millivolt produced a deflection of 10 mm on the record The results in this series, showing that 37 per cent of persons had decreased ventricular complexes, are in keeping with those of other workers,⁵ who have shown that abnormally low voltage is common in elderly persons and that when noted in earlier life it strongly suggests degenerative cardiac disease if other causes of low

TABLE 2—*Electrocardiographic Findings in 100 Persons over 70 Years of Age with Clinically Normal Cardiovascular Systems*

			Persons	
1	Axis deviation	Left	62	
		Right	0	
		Normal	38	
2	Voltage of the major deflection	Abnormally low	37	
		Normal	63	
3	Sino auricular nodal variations	Bradycardia	13	
		Tachycardia	1	
4	Auricular arrhythmias	Fibrillation	3	}
		Flutter	0	
5	Ectopic beats	Auricular	5	}
		Ventricular	15	
6	Auriculoventricular conduction defects	Complete	0	}
		Partial latent	40	
7	Intraventricular conduction defects *	Common form (left bundle branch block)	6	}
		Uncommon form (right bundle branch block)	0	
		Intermediate forms concordant	6	
		"S" type	8	
		Arboration	4	
8	QT type in lead I (anterior)		1	
9	QT type in lead III (posterior)		5	
10	Elevation of ST interval	Lead I	2	}
		Lead III	2	
11	Inversion or abnormal depression of T waves	Lead I only	19	}
		Leads I, II	2	
		Leads I, II, III	5	
		Lead IV-F	5	
12	Presence of Q wave in lead IV-F		18	
13	Normal limits		15	

* Kaplan, L G , and Katz, L N , Am Heart J 18 : 145, 1939

action currents, such as pericaudial disease and technical changes, can be eliminated

Sinus Rhythms—The record of only 1 person revealed a sinus mechanism with a rate exceeding 100 per minute, 13 recordings were under 60 per minute Sinus bradycardia frequently occurred in association with low voltage and partial latent auriculoventricular block No persons known to have hyperthyroidism were included in the series,

5 Levitt, G The Electrocardiogram in the Aged, Am Heart J 18 692, 1939 Cohn¹

although it is our clinical experience that the incidence of hypothyroidism may be rather high in aged persons, especially in women, and that it may be a rather occult condition which easily escapes observation in a routine physical examination. The one person whose rate exceeded the upper limits of normal had sinus tachycardia of 120 beats per minute and was suspected of having hyperthyroidism. It would appear from a study of this series that abnormally rapid sinus mechanisms occur so infrequently that they warrant investigation when discovered in persons over 70 years of age.

Auricular Arrhythmias—No case of auricular flutter was encountered. Auricular fibrillation occurred in 3 persons whose ventricular rates were 90, 92 and 110 respectively. It is interesting to note that

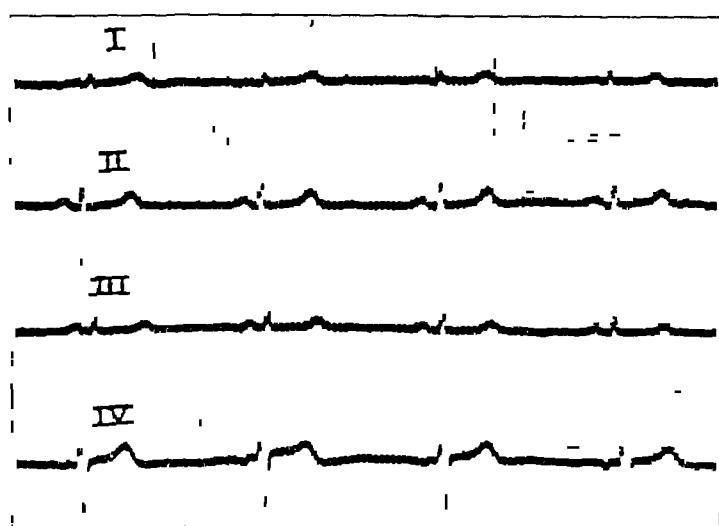


Fig 1—Electrocardiogram including lead IV F, showing the abnormally low voltage of the major deflection and the sinus bradycardia frequently observed in later life. The person was a 78 year old, active, employed man, asymptomatic, with a blood pressure of 140 mm of mercury systolic and 85 mm diastolic and normal cardiac sounds. The size and shape of the heart were found to be normal on roentgenologic examination. The vital capacity was 3,000 cc.

none of these 3 had any other electrocardiographic abnormality. None had ever received digitalis, and the rhythms were entirely asymptomatic. None was able to recall the onset of auricular fibrillation, having had no anginal symptoms, which so often are associated with change from sinus rhythm to auricular fibrillation⁶. The absence of manifestations of congestive failure suggests that the difficulties so often associated with auricular fibrillation may be a result of the exciting cause and not of the arrhythmia itself, this certainly is so when the ventricular rate does not exceed an efficient one.

⁶ White, P. D. Heart Disease, New York, The Macmillan Company, 1938, p 641.

Ectopic Beats—Auricular ectopic beats were noted in 5 persons and ventricular premature beats, including those of nodal origin, in 15 of the 100 persons studied. All 20 were asymptomatic. Two instances of the ventricular type arose from multiple foci. The ectopic beats were not necessarily accompanied by the other changes usually associated with myocardial damage. Apparently this irregularity is of no more clinical significance in the aged than in other age groups except that it seems less prone to produce symptoms.

Auriculoventricular Conduction Defects—Complete auriculoventricular dissociation was observed in none of the persons. It was noted in 1 person who was not included in the series because he had well defined rheumatic heart disease with mitral stenosis and hypertension. Partial

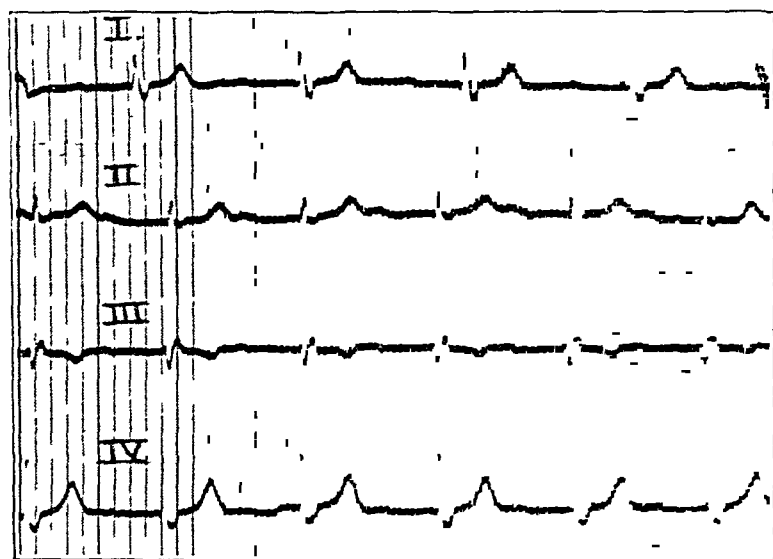


Fig 2—Electrocardiogram including lead IV F, showing moderately decreased voltage of the major deflection, left axis deviation and partial latent auriculoventricular conduction defect. The person was an 80 year old, active, employed man, asymptomatic, with normal blood pressure and normal cardiac sounds. The size and shape of the heart were found to be normal on roentgenologic examination. The vital capacity was 3,300 cc.

latent auriculoventricular blocks, that is, conduction times exceeding 0.20 second, were observed in 40 persons (fig 2). The occurrence of this abnormality in association with sinus bradycardia is not merely coincidental but would seem to be in keeping with the physiologic state of senility observed electrocardiographically in the form of low voltage, sinus bradycardia and auriculoventricular conduction defects.

Intraventricular Conduction Defects—Under this heading are included the complete bundle branch blocks. Six instances of the common (left) form were found, of which 1 was associated with partial auriculoventricular block. No persons presented the uncommon (right) form. Of interest are 3 other examples of the common form which

were recorded on film but were found in persons whose symptoms precluded their inclusion in this series. The symptoms in the 6 persons included were inconsequential and suggested that bundle branch block is not necessarily a serious lesion.⁷ Although the actual duration of the lesion in these persons was unknown, one would suspect that it had been in existence over a year. No fatalities were encountered in this group within eight months after the abnormality was first detected.

Of a total of 24 persons with intraventricular conduction defects, the indeterminate form was observed in 18. This form was further divided into the concordant type, which was noted in 6, the "S" type, in 8 and the arborization type, in 4 of the persons with the indeterminate form of intraventricular conduction defects.

QT Type in Lead I (Anterior)—The type of the QT change in lead I which has been noted to be characteristic of an anterior coronary occlusion⁸ was observed in only 1 instance. In addition, a prominent initial ventricular deflection and an upright T wave in lead IV F as well as ventricular ectopic beats were noted. The record was that of an 81 year old active man whose past history revealed nothing that could be interpreted as having been referable to coronary sclerosis.

QT Type in Lead III (Posterior)—Five instances of the electrocardiographic changes commonly associated with posterior coronary occlusion were observed.

Elevation of the ST Interval—Four instances of ST intervals above the base line were observed. Two were seen in lead I and 2 in lead III. None was associated with an abnormality in the precordial lead.

Inversion or Abnormal Depression of the T Waves—The T wave of lead I alone was flattened or inverted in 19 cases. In 2 cases it was abnormal in both leads I and II, and in 5 cases the three standard leads were involved. Inversion of the T wave in lead IV F alone was found in 5 cases. In 31 cases abnormalities of 1 or more T waves were observed. These excluded the T wave in lead III alone which is not generally considered pathologic, especially in the presence of left axis deviation.⁹

7 Sampson, J. J., and Nagle, O. E. The Prognosis of Bundle Branch Block and Other Intraventricular Conduction System Lesions, *Am J M Sc* **191** 88, 1936. Bishop, L. F., and Bishop, L. F., Jr. Bundle Branch Block of Unusual Duration, *J A M A* **98** 398 (Jan 30) 1932. Kaplan, L. G., and Katz, L. N. Prognosis of Intraventricular Block, *Am Heart J* **18** 145, 1939.

8 Parkinson, J., and Bedford, D. K. Cardiac Infarction and Coronary Thrombosis. Successive Changes in the Electrocardiogram, *Heart* **14** 195, 1928. Smith, F. M. Electrocardiographic Changes Following Occlusion of the Left Coronary Artery, *Arch Int Med* **32** 497 (Oct) 1923.

9 Berliner, K., and Master, A. Mitral Stenosis. A Correlation of Electrocardiographic and Pathologic Observations, *Arch Int Med* **61** 39 (Jan) 1938.

Q Wave in Lead IV F—A prominent initial ventricular deflection in lead IV F was noted in 18 persons. In 5 of these it was associated with intraventricular conduction defects. In 1 it occurred with inversion of the T wave in leads I, II and III. The remaining 12 were isolated examples of prominence of the Q wave in lead IV F. One of these persons was a 75 year old active waiter whose past history was not significant, he had a negative Wassermann reaction of the blood and a blood pressure of 150 mm of mercury systolic and 80 mm diastolic. The area of cardiac dulness was slightly enlarged, the cardiac sounds were normal and there was no evidence of congestive failure. Two months following the examination he died after an attack of bronchopneumonia resulting from an alcoholic episode. Postmortem examination revealed an area of localized constriction in the left anterior descending coronary artery at a level 2 cm distal to the bifurcation of the left anterior coronary artery. An area of cardiac infarction included the apex of the heart, it was an old lesion, and no recent areas of myomalacia were observed. Bilateral bronchopneumonia was the evident cause of death. Arteriosclerosis was advanced in all vessels and was principally of the cential type. It is of interest to note that this death was the only one that occurred in the series within eight months of study. No cardiovascular lesions of any sort have been discovered although all persons included in the series have been under personal observation and all have received regular follow-up examinations since the beginning of the study.

In 3 persons both a prominent Q wave and an inverted T wave in lead IV F were encountered. One of them had the right axis deviation and the second had the rheumatic heart disease with complete auriculo-ventricular dissociation previously commented on. The third had had acute coronary occlusion three years previously. These 3 persons were not included in the series. Their cases strongly suggested that the presence of a prominent downward initial ventricular deflection in combination with an inversion of the T wave in lead IV F is indicative of cardiac disease.

Electrocardiograms Within Normal Limits—Electrocardiograms which are considered to be within normal limits were noted in 15 persons. Those records which presented ectopic beats from a single focus, either auricular or ventricular, or sinus bradycardia with a rate exceeding 50 beats per minute when uncomplicated by other conditions were not considered sufficiently abnormal to be excluded. Because of observations of other investigators,⁵ the inclusion, in the so-called normal group, of persons with partial auriculoventricular conduction defects or abnormally low voltage was not considered strictly correct. Although in elderly persons these conditions were commonly found, they have generally been associated with a deficient coronary circula-

tion Especially abnormally low voltage, when noted in younger age groups, is generally considered ¹⁰ a sign of extensive myocardial involvement In this series, however, abnormally low voltage is compatible with a relatively normal functional capacity for the age group It was noted in 37 per cent of all persons, and seldom was associated with the electrocardiographic observations usually assumed to be consistent with myocardial damage

COMMENT

It is apparent that many, if not all, of these electrocardiographic changes are probably the result of minor silent coronary occlusions The more extensive changes recorded may well be a manifestation of repeated episodes of this type occurring not only asymptotically but also without objective clinical evidence Which of these electrocardiograms represent the result of small fibrotic cardiac lesions following silent, acute coronary occlusions and which represent the slow, gradual process of narrowing of the coronary arteries is impossible to determine It is reasonable to assume, however, that these records revealing evidences of myocardial disease which in younger persons are associated with acute coronary thrombosis are caused by a similar process in later life

According to the data presented, the electrocardiogram in the older age group must be interpreted with greater care than in children or in the middle-aged group, and the usual standards of normalcy cannot be adhered to too strictly Only 15 per cent of the persons in this series, consisting of active asymptomatic persons over 70 year of age, presented a normal electrocardiogram by the usual standards

In a person over 70 years of age who is suspected of having a cardiac disorder, especially an acute coronary occlusion, certain observations may be considered of value in corroborating the diagnosis Such findings are the electrocardiographic changes associated with manifestations of cardiac disease which were observed in the persons whose cases were described but who were excluded from this series Among the lesions that occurred together with inadequate cardiac function or anginal pain were complete auriculoventricular block, which was noted in the person with rheumatic heart disease, and bundle branch block (common form), which was noted in 3 persons

Right axis deviation was not observed in any of the persons reported on and should be considered a pathologic lesion in the age group studied Left axis deviation, on the other hand, was noted in 62 per cent of the persons in this series

The QT type of electrocardiogram in lead I which is usually considered a sign of anterior coronary occlusion was encountered but once in

¹⁰ White,⁶ p 128

this series and therefore may be regarded as significant. The type of QT change in lead III (the posterior group) was noted five times and would seem to demand greater attention although it is consistent with unrestricted activity. An ST interval above the base line was found in 2 instances in leads I and III, although this change is difficult to interpret, it is not necessarily one¹¹ to be viewed with alarm in this age group.

Inversion of the T wave in any or all leads was common in this series, occurring in 31 per cent of the persons, and hence was not significant. However, the occurrence of an inverted T wave in lead IV F associated with a prominent Q wave in lead IV is a combination frequently identified with myocardial damage. Incidentally, the occurrence of a prominent Q wave in lead IV F alone is of little significance, although in 5 of the 18 persons studied it was accompanied by intraventricular conduction defects. Slow, untreated auricular fibrillation not only appears to be of minor importance in itself but usually does not occur with other changes suggesting cardiac disease. In contradistinction to the rapid ventricular rates in untreated auricular fibrillation in younger age groups, the presence of an auriculoventricular block so frequently observed in the aged may obviate the rapid ventricular rate. This occurrence may explain the absence of any noticeable disability from auricular fibrillation in the cardiac mechanism in later life.

In summary, it may be stated that in attempting to establish a base line for an electrocardiogram of persons over 70 years of age, left axis deviation, unusually low voltage, partial latent auriculoventricular conduction defects and inverted or depressed T waves in any or all leads may be considered normal. Other cardiographic changes observed in this series of apparently normal persons were considerable sinus bradycardia in 13 per cent, intraventricular conduction defects in 24 per cent, and prominence of the Q wave in lead IV F in 18 per cent. These are conditions which in a younger age group would not be considered normal. Only 15 per cent of the persons were considered to have normal electrocardiograms, and these included persons presenting ectopic beats from a single focus and/or sinus bradycardia with a rate exceeding 50 beats per minute in the absence of other complications. If persons having these two arrhythmias were to be excluded, only 12 per cent of the electrocardiograms could be interpreted as normal by the usual criteria.

SUMMARY AND CONCLUSIONS

A group of 100 active, employable, asymptomatic persons between the ages of 70 and 92 years, who presented no clinical evidence of

11 Bohning, A., and Katz, L. N. Unusual Changes in the Electrocardiogram of Patients with Recent Coronary Occlusion, *Am J M Sc* **186** 39, 1933

cardiac disease other than systolic mitral murmurs of the arteriosclerotic type and slow, untreated auricular fibrillation, were examined electrocardiographically

Certain electrocardiograms which are usually considered pathologic occurred with sufficient frequency to be considered normal for this age group. They included records of left axis deviation, abnormally low voltage, sinus bradycardia, partial latent auriculoventricular conduction defects, intraventricular conduction defects and inversion and flattening of the T waves in any or all leads.

Some changes occurred in a sufficiently small percentage of persons to warrant the impression that when noted they could be considered only presumptive evidence of myocardial disease. These were auricular fibrillation, bundle branch block, elevation of the ST intervals above the base line, especially in the first standard lead, and the occurrence of the type of QT changes in lead I associated with anterior coronary occlusion.

Definite abnormalities of the cardiovascular system were suggested by electrocardiographic changes in which a prominent Q wave was observed in association with an inversion of the T wave in lead IV F, complete auriculoventricular dissociation and right axis deviation.

It is intimated that greater care must be taken in the interpretation of the electrocardiograms of persons in later life than in the interpretation of those of the younger age groups if errors of commission are to be avoided in the diagnosis of acute lesions of the coronary arteries.

DIFFERENTIATION OF ACUTE CORONARY INSUFFICIENCY WITH MYOCARDIAL INFARCTION FROM CORONARY OCCLUSION

ARTHUR M MASTER, M D

RICHARD GUBNER, M D

SIMON DACK, M D

AND

HARRY L JAFFE, M D

NEW YORK

For some time a transitory insufficiency of the coronary blood flow has been accepted as the physiologic basis for the anginal syndrome. Only recently,¹ however, has it been sufficiently realized in this country that infarction of the myocardium may result from acute coronary insufficiency, in the absence of coronary occlusion or even of coronary sclerosis. The German literature² has emphasized the frequency of cardiac infarction due to coronary insufficiency. In two large series of cases of myocardial infarction studied post mortem, Graef³ and Horn⁴ found recent coronary occlusion in only 60 per cent, the remaining infarcts being associated with coronary insufficiency. Several authors⁵ have stated that in sudden death due to disease of the coronary arteries an acute occlusion frequently is not found.

From the Cardiographic Laboratory, the Mount Sinai Hospital

1 (a) Libman, E. Symposium: Angina Pectoris, with Special Reference to Coronary Artery Disease, General Considerations, *Bull New York Acad Med* **11** 427, 1935. (b) Friedberg, C K., and Horn H. Acute Myocardial Infarction Not Due to Coronary Artery Occlusion, *J A M A* **112** 1675 (April 29) 1939. (c) Gross, H., and Sternberg, W H. Myocardial Infarction Without Significant Lesions of Coronary Arteries, *Arch Int Med* **64** 249 (Aug) 1939.

2 (a) Buchner, F., Weber, A., and Haager, B. Koronarinfarkt und Koronarinsuffizienz in vergleichender elektrokardiographischer und morphologischer Untersuchung, Leipzig, Georg Thieme, 1935. (b) Dietrich, S., and Schwiegk, H. Das Schmerzproblem der Angina pectoris, *Klin Wchnschr* **12** 135, 1933.

3 Graef, I. Personal communication to the authors.

4 Horn, H. Personal communication to the authors.

5 (a) Levy, R L., and Bruenn, H G. Acute, Fatal Coronary Insufficiency, *J A M A* **106** 1080 (March 28) 1936. (b) Halpern, M. Personal communication to the authors. (c) Buchner, F. Die Deutung des Elektrokardiogramms bei den Durchblutungsstörungen des Herzmuskels, *Klin Wchnschr* **17** 1713, 1938.

These two types of infarction differ sharply in their pathogenesis and in the pathologic changes they present. Occlusion of a coronary artery is the end result of a progressive process in a sclerotic vessel. It is followed, as a rule, by a relatively large confluent area of infarction extending through and through from endocardium to pericardium. Coronary insufficiency, on the other hand, exists whenever a disproportion arises between the oxygen requirements of the heart and the coronary blood flow, it is provoked by factors which increase the work of the heart or reduce the coronary circulation. This concept was clearly stated by Hall⁶ as early as 1842. If the inadequacy of coronary flow is of sufficient duration or degree, the ischemia results in irreversible changes in the myocardium. This type of infarction differs from that following coronary occlusion in that it consists usually of disseminated foci of myomalacia and is largely subendocardial, involving particularly the papillary muscles and interventricular septum. There are very rare exceptions in which there are extensive areas of infarction.

In spite of these differences in pathogenesis and morphology, the clinical features of myocardial infarction due to coronary insufficiency may be similar to those of infarction following coronary occlusion, and the two conditions may be confused. Since myocardial infarction following coronary insufficiency is now known to be common, the differential diagnosis from occlusion is important. It seemed to some of us⁷ that there might be differences in the electrocardiogram since the pathologic changes in the two conditions were distinct. Buchner⁸ found depression of the RS-T segment and changes in the T wave in his cases of coronary insufficiency in contradistinction to the elevation of the RS-T segment observed in coronary occlusion. It was the purpose of this study to determine the frequency of such electrocardiographic changes and their value in differential diagnosis.

MATERIAL

Forty-eight fatal cases were studied in which necropsy showed recent myomalacia without acute coronary occlusion. The coronary arteries were examined throughout their course with extreme care, being cut horizontally at intervals of 2 to 3 mm. Numerous sections of the arteries and myocardium were studied microscopically.^{1b} Coronary sclerosis was present in the majority of cases, and cardiac enlargement was common.

6 Hall, M. On the Mutual Relation Between Anatomy, Physiology, Pathology and Therapeutics and the Practice of Medicine. Being the Gulstonian Lectures for 1842, London, H. Baillière, 1842, p. xii.

7 (a) Master, A. M., Dack, S., and Jaffe, H. L. Activities Associated with the Onset of Acute Coronary Artery Occlusion, *Am Heart J* **18** 434, 1939. (b) Master, A. M., and Jaffe, H. L. Coronary Insufficiency and Myocardial Necrosis Due to Acute Hemorrhage, *J Mt Sinai Hosp* **7** 26, 1940.

8 Buchner, Weber and Haager^{2a} Buchner^{5c}

Our series included cases illustrating the common causes of acute coronary insufficiency. The causes could be divided roughly into two groups, those resulting in greatly increased work of the heart and those producing a reduction in coronary blood flow. Among the former were heart failure (11 cases), aortic stenosis (4 cases),⁹ hypertensive crises (4 cases), postoperative complications (7 cases)¹⁰ and infection (4 cases). The second group comprised acute loss of blood (5 cases),^{7b} severe anemia (1 case), heart block (1 case), heart failure (11 cases),¹¹ shock following operation (7 cases),¹⁰ an acute condition in the abdomen (2 cases), cerebral hemorrhage (2 cases), pulmonary embolism (3 cases)¹² and cor pulmonale due to emphysema (3 cases). Tachycardia, which also produces coronary insufficiency, was present in the majority of cases.

Electrocardiograms were acceptable for study in 23 cases, since the changes encountered could be attributed directly to the episode of acute coronary insufficiency. In 14 of these, control records were obtained prior to the attack. In the other 9 cases electrocardiograms were obtained after the attack only, but the abnormalities were certainly produced by the coronary insufficiency since changes occurred from day to day and no evidence of preexisting disease was found at necropsy. The electrocardiograms in the remaining 25 cases were not included in this report since the changes could not be ascribed with certainty to coronary insufficiency because of the presence of chronic heart disease or because digitalis had been administered in several cases. It is probable that in at least some of these cases the alterations in the electrocardiogram were due to coronary insufficiency, since they resembled those observed in the accepted group.

Several illustrative cases will be cited.

CASE 1—*Myocardial infarction without coronary occlusion following operation*

N. R., a man aged 63, entered the hospital with symptoms of prostatic hypertrophy. There was no history of angina pectoris or dyspnea. The heart was not enlarged. The blood pressure was 138 systolic and 78 diastolic. The electrocardiogram (fig 1A) showed only slight slurring of the QRS complex, which measured 0.10 second in duration. A first stage suprapubic prostatectomy was done, and several days afterward the patient had transitory precordial pain. At this time the electrocardiogram (fig 1B) exhibited a distinct depression of the RS-T segment in leads I, II and IV. The T waves were flattened in leads I and II and inverted in lead III. Two days later a second stage prostatectomy was performed, after which the course was uneventful except for considerable fever for several days. On the fourteenth postoperative day the patient was seized with severe precordial pain and went into shock, the blood pressure falling to 80 systolic and 60 diastolic. There were rales at the bases of both lungs. The elec-

9 Master, A. M., Jaffe, H. L., and Dack, S. An Electrocardiogram Characteristic of Coronary Thrombosis in a Patient with Aortic Stenosis, *J. Mt. Sinai Hosp.* **4**: 138, 1937.

10 Master, A. M., Dack, S., and Jaffe, H. L. Postoperative Coronary Artery Occlusion, *J. A. M. A.* **110**: 1415 (April 30) 1938.

11 Visscher, M. B. The Restriction of the Coronary Flow as a General Factor in Heart Failure, *J. A. M. A.* **113**: 987 (Sept. 9) 1939.

12 Horn, H., Dack, S., and Friedberg, C. K. The Cardiac Sequelae of Embolism of the Pulmonary Artery, *Arch. Int. Med.* **64**: 296 (Aug.) 1939.

trocardiogram (fig 1 C) now showed definite inversion of the T wave in leads II and III, with persistent depression of the RS-T interval in the standard leads. The patient recovered within half an hour, and his condition was satisfactory until the next day when a similar episode occurred, which ended fatally. At post-mortem examination acute myomalacia of the posterior wall and posterior papillary muscle of the left ventricle was found. The coronary arteries were sclerotic and severely narrowed, but no recent occlusion was present.

CASE 2—Myocardial infarction without coronary occlusion following cardiac failure in aortic stenosis

P. K., a woman aged 65, was admitted to the hospital in 1931 because of myocardial failure associated with aortic stenosis of undetermined cause. The electrocardiogram was typical of a large left ventricle (fig 2 A). During the next five years the patient was in a condition of mild congestive failure. Two weeks before the present admission she had an attack of precordial pain lasting two days.

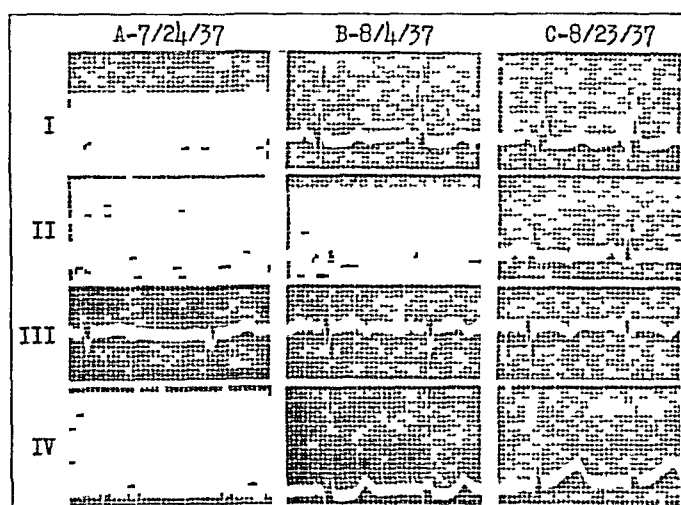


Fig 1—Case 1, N. R., a man aged 63, had myocardial infarction without coronary occlusion after prostatectomy. *A*, the preoperative electrocardiogram was normal except for a small Q wave in lead I and a slight slurring of the QRS complex, which measured 0.10 second in duration. *B*, in a record made eight days after a first stage prostatectomy the RS-T interval was depressed in leads I, II and IV and the T wave was lower in leads I and II and semi-inverted in lead III. *C*, in a record made fourteen days after a second stage prostatectomy and immediately after an attack of acute coronary insufficiency the RS-T interval was still depressed in standard leads and the T wave was definitely inverted in leads II and III. The clinical course simulated acute coronary occlusion. Postmortem examination revealed acute and organizing infarction of the posterior wall of the left ventricle. The coronary arteries were sclerotic, but no recent occlusion was present.

This was followed by expectoration of bloody sputum and by fever. The diagnosis was coronary occlusion, aortic stenosis, auricular fibrillation and cardiac failure. The white blood cell count was 32,000, and the temperature was 102 F. The electrocardiogram (fig 2 B) showed auricular flutter with complete auriculo-ventricular dissociation and marked depression of the RS-T segment in leads I and IV. Postmortem examination showed microscopic areas of myocardial infarction.

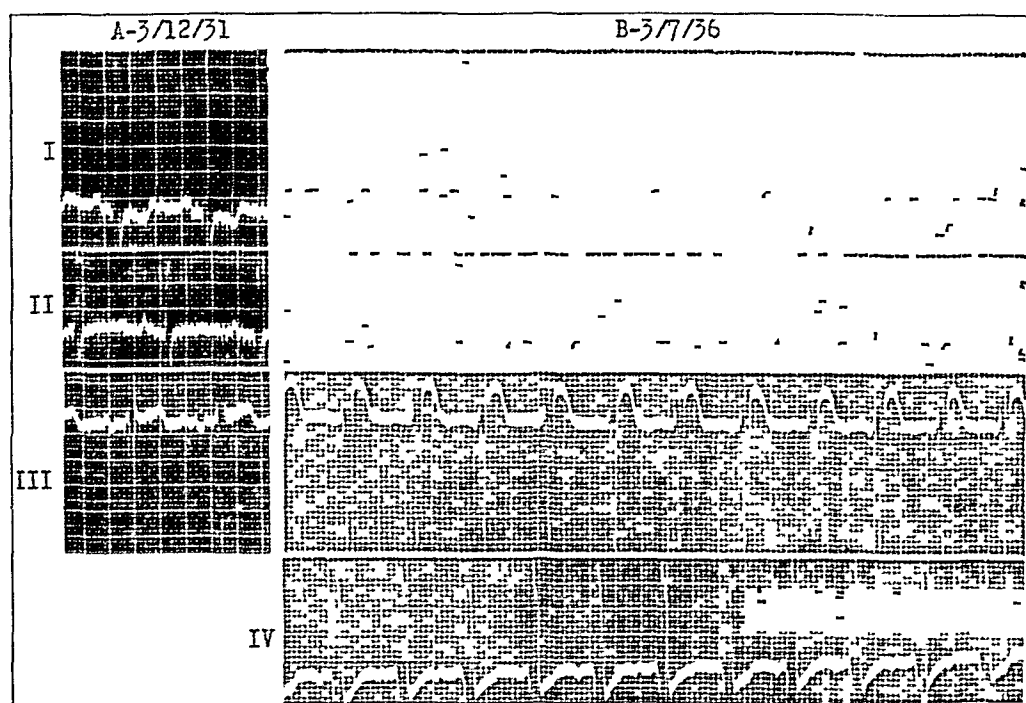


Fig 2—Case 2, P K a woman aged 65, had coronary insufficiency due to calcific aortic stenosis and congestive heart failure. The clinical course suggested acute coronary occlusion. A, a control electrocardiogram taken five years ago showed marked left axis deviation, high voltage of the QRS complex, depression of the ST interval in lead I and elevation in lead III and inversion of the T wave in lead I and flattening in lead II. This pattern is characteristic of a very large left ventricle such as is seen in aortic stenosis. B, in a record made after an attack of acute coronary insufficiency there was a marked depression of the ST interval in leads I and IV and an increased elevation in lead III. Auricular flutter with auriculo-ventricular dissociation and a regular idioventricular rate of 120 were present. Postmortem examination showed "fish mouth" aortic stenosis. The coronary arteries were normal. The myocardium revealed microscopic areas of necrosis.

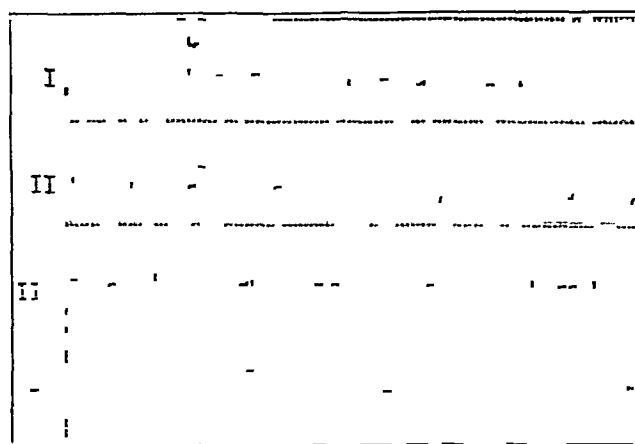


Fig 3—Case 3, T L, a woman aged 19, had myomalacia following severe intestinal hemorrhage in ulcerative colitis. The electrocardiogram showed depression of the ST interval and marked flattening of the T wave in the standard leads. Postmortem examination revealed disseminated areas of myocardial necrosis chiefly in the papillary muscles of the left ventricle. The coronary arteries were normal.

tion, although the coronary arteries were relatively normal. There was chronic rheumatic valvular disease with mitral stenosis and insufficiency and "fish mouth" aortic stenosis. The heart was generally hypertrophied.

CASE 3—*Acute myomalacia following intestinal hemorrhage in ulcerative colitis*

T L, a woman of 19, without previous evidence of heart disease, entered the hospital in a condition of profound anemia caused by bloody diarrhea on the basis of ulcerative colitis. The hemoglobin content was only 14 per cent, and the red blood cells numbered 750,000 per cubic millimeter. Marked tachycardia, gallop rhythm, a harsh systolic murmur over the precordium and rales at the bases of the lungs were present. The electrocardiogram (fig 3) showed depression of the RS-T segment and flattening of the T wave in the three standard leads. Postmortem examination revealed scattered foci of myocardial necrosis involving chiefly the papillary muscles of the left ventricle. The coronary arteries were entirely normal.

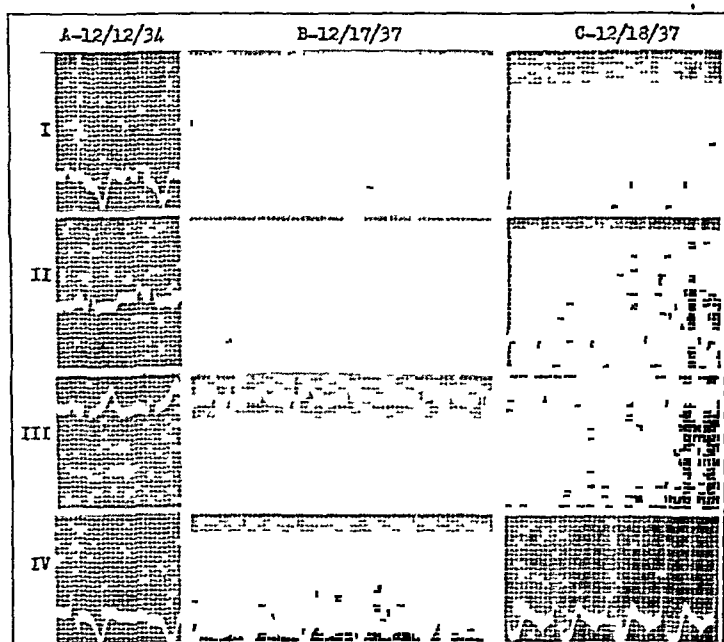


Fig 4—A F, a woman aged 53, with long-standing hypertensive heart disease, had myocardial infarction following recurrent pulmonary embolism. A, a control electrocardiogram made three years ago revealed a typical hypertensive pattern. There was marked left axis deviation, high voltage of the QRS complex, depression of the ST interval in leads I and II and deep inversion of the T wave in leads I, II and IV. B, in an electrocardiogram made after pulmonary embolism which clinically simulated coronary occlusion, the depression of the ST interval was more marked in leads I, II and IV and there was an incomplete auriculo-ventricular dissociation with dropped beats. C, in the electrocardiogram made the next day the depression of the ST interval was more marked in all leads. Sinus tachycardia with a rate of 135 was now present. Postmortem examination revealed recurrent embolism of the main branches of the pulmonary artery. The myocardium showed focal areas of subendocardial necrosis particularly in the left ventricle. The coronary arteries showed only slight sclerosis without narrowing or occlusion.

RESULTS

Clinical Features—Frequently the symptoms and signs of acute coronary insufficiency are identical with those of acute coronary occlusion. The onset may be abrupt, with severe precordial pain, collapse and vomiting, followed by heart failure, changes in the heart sounds, drop in blood pressure, fever, leukocytosis, etc. However, the attack of coronary insufficiency could often be suspected clinically owing to the presence of a definite precipitating factor, such as operation, shock, acute hemorrhage or aortic stenosis. This in turn might mask some or all of the symptoms of the attack. Thus a patient in shock or under sedation after operation may not be alert to precordial pain. There-

*Summary of Electrocardiographic Findings in Coronary Insufficiency
with Infarction (23 Cases)*

Rhythm—Sinus tachycardia	18				
Auricular bigeminy	1				
Ventricular extrasystoles	1				
Auricular flutter	1				
Complete auriculoventricular dissociation	1				
Incomplete auriculoventricular dissociation with dropped beats	1				
Axis deviation					
No significant change	19				
Right axis deviation	1				
Left axis deviation disappeared	2				
PR interval					
Normal	18				
Prolonged to 0.30 second	1				
Prolonged to 0.21 to 0.24 second	4				
QRS complex					
Slurring and widening to 0.13 second	4				
	No	Lead I	Lead II	Lead III	Lead IV
Q wave	7	0	2	3	3
RS-T depression	15	15	14	11	7
RS-T elevation	6	1	3	5	4
T wave changes	20				
Became inverted		8	10	11	5
Became flattened		2	0	3	1
Became upright		3	3	0	0

fore, the first sign of infarction due to coronary insufficiency may be a sudden drop in blood pressure or the sudden appearance of heart failure.

In the majority of cases signs of previous heart disease were evident. Hypertension, cardiac enlargement, severe coronary sclerosis and previous heart failure were common. Long-standing aortic valvular disease was present in 5 cases.

The Electrocardiogram—More than one record, including the precordial lead, was obtained in each case, the average number was two. They were taken before the agonal stage had set in. In 14 cases control electrocardiograms taken before the attack of coronary insufficiency were available. The findings are summarized in the table.

The outstanding deviations in the electrocardiogram were a depression of the RS-T segment of 1 mm or more and a slight inversion of

the T wave in two or more leads. These were present in 20 of the 23 cases. The changes were equally common in the first, second and third leads but occurred in less than half of the cases in the precordial lead. They usually appeared soon after the attack of coronary insufficiency and in these fatal cases persisted until death, which occurred usually within a week. Not infrequently the depression of the RS-T segment was marked and the T wave definitely inverted, although a very deeply inverted or cove plane T wave was not observed. As a rule the changes were maximal on their initial appearance and only occasionally progressed.

In contrast to the frequency of depression of the RS-T segment, elevation of this segment was infrequent, occurring only 6 times. It

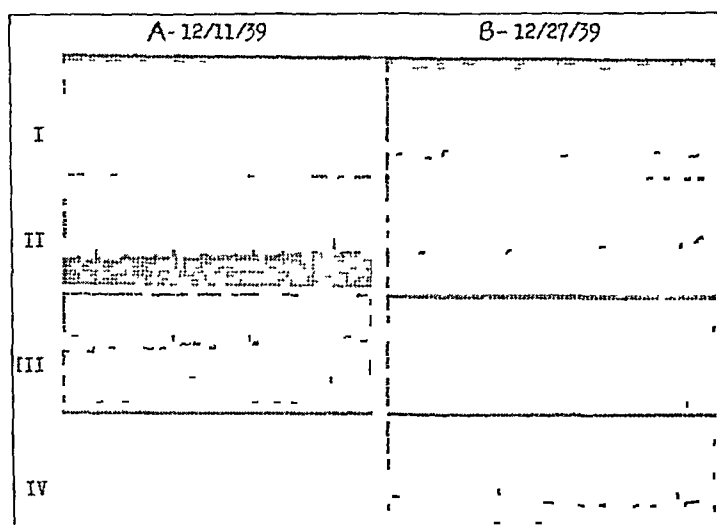


Fig 5—R. K., a woman aged 55, had bleeding peptic ulcer with precordial pain due to coronary insufficiency. *A*, in an electrocardiogram, made during the stage of acute anemia when the hemoglobin content was 39 per cent, there was left axis deviation and slurring of the QRS complex, the ST interval was depressed in leads I and II and the T wave was semi-inverted in lead I and flattened in II and IV. *B*, in an electrocardiogram made after the cessation of bleeding and several blood transfusions, when the hemoglobin content was 68 per cent and precordial pain was no longer present, the ST interval was only slightly depressed in lead I and the T wave was upright and of normal amplitude in leads I, II and IV.

was most often present in the third lead and usually was accompanied by reciprocal depression in the first lead. It was never marked. Elevation of the RS-T segment in lead I occurred only once.

Another striking negative finding in coronary insufficiency, in contrast to coronary occlusion, was the paucity of Q waves, which were observed only 7 times. Not once was a Q wave encountered in the first lead. In 1 case it is possible that the Q wave in leads II and III preceded the episode of coronary insufficiency.

Other abnormalities in the electrocardiogram occurring after coronary insufficiency were uncommon. Sinus tachycardia was constant. Auricular bigeminy, ventricular extrasystoles, auricular flutter and complete and incomplete auriculoventricular dissociation each occurred once. In 1 case the PR interval became prolonged to 0.30 second, in another case to 0.24 second and in 3 cases it was 0.21 to 0.23 second. In 2 cases left axis deviation disappeared, and in 1 right axis deviation set in accompanied by heart failure. In 4 cases the QRS complex became slurred and widened to 0.13 second under observation. In 8 other cases slurring may have been present prior to the attack.

Nonfatal Coronary Insufficiency—In addition to the cases reported, we have made the diagnosis of coronary insufficiency with infarction in a number of patients who survived, from the typical electrocardiographic changes and usually a precipitating factor, such as cerebral hemorrhage, peptic ulcer with acute hemorrhage (fig 5) or an operation. In the cases of some of these patients the course was mild or even asymptomatic, and the electrocardiogram returned to normal within a week or two. In others the episode simulated acute coronary occlusion or severe angina pectoris. It is our impression that in the past such conditions were labeled small coronary occlusions. However, the mild course, the presence of depression instead of elevation of the RS-T interval and the rapid return of the electrocardiogram to normal (fig 5) suggested the presence of coronary insufficiency and not coronary occlusion.

COMMENT

The electrocardiogram in acute coronary insufficiency with infarction is characterized by the presence of a depressed RS-T interval and changes in the T wave, and by the absence of an elevated RS-T interval and a Q wave. It thus differs very definitely from the usual patterns observed in coronary occlusion. In 250 cases of the latter, elevation of the RS-T segment was present in 85 per cent and a Q wave in 89 per cent, only 7 per cent of the cases showed neither a Q wave nor an elevation of the RS-T interval. In addition, a reciprocal relationship existed between elevation in lead I and depression in lead III in anterior infarction and vice versa in posterior infarction. Hence as a rule the electrocardiogram differentiates myocardial infarction due to coronary insufficiency from that due to coronary occlusion. Occasionally, however, the electrocardiogram in either condition is atypical and not diagnostic. Thus, in 6 out of 100 cases of coronary occlusion in which the diagnosis was confirmed at necropsy there was depression of the RS-T segment in all leads without elevation. Also, sometimes only changes in the T wave, without deviations in the RS-T segment, are observed in coronary occlusion. On the other hand, we have seen that in coronary insufficiency a Q wave or slight elevation of the RS-T segment is

present occasionally in lead III or IV. However, these are exceptional cases, and we believe a useful rule is the following: When a Q wave or elevation of the RS-T segment is present, especially in lead I or II, the condition is coronary occlusion with infarction, when depression of the RS-T segment alone is present, the cause is probably coronary insufficiency without occlusion.

The differences in the electrocardiogram in coronary insufficiency and coronary occlusion can be explained by the dissimilar pathologic changes. It has been suggested¹³ that the elevation of the RS-T segment in coronary occlusion is associated with pericardial involvement, which is common in this condition. In coronary insufficiency, the areas of necrosis are focal and scattered and chiefly subendocardial, the pericardium is spared. Therefore, elevation of the RS-T interval is absent and is replaced by depression. Recently Boyd and Scherf¹⁴ have shown that injury to the epicardium at the apex of the heart produces a high take-off of the RS-T segment, whereas injury to the endocardium produces depression of this segment with slight inversion of the T wave.

That depression of the RS-T segment is due to coronary insufficiency receives confirmation in the observations following induced effort¹⁵ or rebreathing¹⁶ and the administration of epinephrine or insulin. These procedures increase the work of the heart or diminish the coronary flow and therefore, in persons with coronary disease, frequently result in a state of coronary insufficiency. Actually, they may produce transient depression of the RS-T segment in the electrocardiogram, which may be employed as a diagnostic test of coronary disease.

Coronary insufficiency of greater or lesser degree is probably extremely common. Its clinical significance depends on its severity and on the degree of preexisting cardiac involvement. When the disproportion between cardiac demand and coronary flow is mild and if the heart is normal or only slightly involved by preexisting disease, there may be no symptoms or the patient may suffer a mild anginal attack. This is usually of short duration and is probably unaccompanied by any structural change in the myocardium. Thus, after operation, we

13 Pezzi, C., Defrise, A., and Agostoni, G. L'onde en dôme coronarienne de Smith et Pardee chez le chien, recherches expérimentales, *Arch d mal du cœur* **30** 929, 1937. Schwab, R. Experimentelle Untersuchungen über die Entstehung des Infarktbildes im Extremitäten-Elektrokardiogramm, *Ztschr f d ges exper Med* **103** 1, 1938.

14 Boyd, L. J., and Scherf, D. The Electrocardiogram After Mechanical Injury of the Inner Surface of the Heart, *Bull New York M Coll, Flower & Fifth Ave Hosps* **3** 4, 1940.

15 Scherf, D., and Goldhammer, S. T. Zur Frühdiagnose der Angina pectoris mit Hilfe des Elektrokardiogrammes, *Ztschr f klin Med* **124** 11, 1933.

16 Katz, L. N., Hamburger, W. W., and Schutz, W. J. The Effect of Generalized Anoxemia on the Electrocardiogram of Normal Subjects, *Am Heart J* **9** 771, 1934.

have observed electrocardiographic changes in patients who have felt well and even walked about without symptoms. However, when the degree of coronary insufficiency and myocardial damage is great, necrosis of the heart muscle takes place and death may result.

The diagnosis of coronary insufficiency, in contradistinction to coronary occlusion, should suggest itself when an episode of severe precordial pain, shock or heart failure is associated with some factor capable of increasing the work of the heart or decreasing the coronary flow. The chief of these precipitating factors are shock following operation, pulmonary embolism or acute hemorrhage, marked tachycardia or bradycardia, impaired oxygen capacity of the blood, as in acute anemia, aortic stenosis or insufficiency, and heart failure itself, associated with slowing of the circulation. We have not observed any instance of coronary insufficiency with myocardial infarction produced by effort or excitement but this sequence seems theoretically possible since the heart rate and blood pressure and therefore the cardiac work are increased. The ordinary anginal syndrome is almost always associated with effort or excitement, if these factors are severe or prolonged and the coronary arteries very sclerotic, the resulting anoxemia may be sufficient to produce necrosis of the muscle.

SUMMARY

A clinical and electrocardiographic study was made of 48 cases of acute coronary insufficiency, i. e., recent myomalacia without acute coronary occlusion.

The myomalacia following coronary insufficiency differs, as a rule, from that following coronary occlusion by its focal and disseminated character and its localization in the subendocardium and papillary muscles of the left ventricle.

Clinically, coronary insufficiency is usually associated with some factor which increases the work of the heart or diminishes the coronary flow, most often in a subject with antecedent cardiac enlargement and coronary sclerosis. The precipitating factors in the series studied included heart failure, shock due to operation, pulmonary embolism, acute hemorrhage and infection, marked tachycardia or bradycardia, acute anemia, aortic valve disease, and hypertensive crises.

The electrocardiogram of acute coronary insufficiency with infarction is characterized by the presence of a depressed RS-T segment and flattening or inversion of the T wave in two or more leads. The occurrence of an elevated RS-T segment or a Q wave, particularly in lead I, is rare. The electrocardiogram thus differs from that of acute coronary occlusion in which the latter changes are common.

The presence of a depressed RS-T segment in acute coronary insufficiency is attributed to the subendocardial localization of the infarction.

HYPERPARATHYROIDISM WITH ADENOMA CAUSING RENAL FAILURE AND SECONDARY HYPERPARATHYROIDISM

REPORT OF A CASE

ROGER S DOWNS, M D

FARMINGTON, CONN

AND

VIRGIL SCOTT, M D

DURHAM, N C

It is well recognized that a serious form of renal disease may result from hyperparathyroidism¹ It is also well established that chronic renal insufficiency frequently is associated with secondary hyperplasia of the parathyroid glands² On a priori grounds, therefore, one can reason that a paradoxical situation might exist wherein long-standing renal disease resulting from a parathyroid adenoma is so severe as to stimulate further overactivity of the other parathyroid glands Actually this does occur Johnson³ reported a case in which removal of a parathyroid adenoma was followed by death from hypertension and uremia four years later, at which time the remaining parathyroid glands showed enlargement and hyperplasia The following case report is submitted because it is the first to our knowledge in which secondary parathyroid hyperplasia has been proved to coexist with a parathyroid adenoma

REPORT OF CASE

A C, a former insurance salesman, aged 50, entered the Rochester Municipal Hospital in May 1938 complaining of attacks of pain in the right flank, an

From the Department of Medicine, University of Rochester School of Medicine and Dentistry, and the Medical Clinics of the Strong Memorial and Rochester Municipal Hospitals

1 Albright, F, Baird, P C, and Bloomberg, E Studies on Physiology of Parathyroid Glands Renal Complications of Hyperparathyroidism, *Am J M Sc* **187** 49-65, 1934

2 (a) Albright, F, Drake, T G, and Sulkowitch, H W Renal Osteitis Fibrosa Cystica Report of Case with Discussion of Metabolic Aspects, *Bull Johns Hopkins Hosp* **60** 377-399, 1937 (b) Castleman, B, and Mallory, T B Parathyroid Hyperplasia in Chronic Renal Insufficiency, *Am J Path* **13** 553-574, 1937 (c) Shelling, D H, and Remsen, D Renal Rickets Report of Case Showing Four Enlarged Parathyroids and Evidence of Parathyroid Hypersecretion, *Bull Johns Hopkins Hosp* **57** 158-181, 1935

3 Johnson, J W, Jr Primary Hyperparathyroidism with Extensive Renal Calcification and Secondary Hyperplasia of the Parathyroids Report of a Case, *Am J Path* **15** 111-123, 1939

ammoniacal taste in the mouth and increasing weakness and fatigability. The attacks of pain began fifteen months before entrance to the hospital, at first occurring infrequently and only momentarily. Just before admission they had been occurring every two weeks and sometimes had lasted as long as eight hours, with radiation of the pain from the flank to the anterior part of the abdomen and to the genitalia. They were frequently accompanied by chills and fever, grossly, bloody urine had been noted in association with the more severe attacks. The patient had lost about 35 pounds (15.9 Kg.) in weight.

Of significance in the past history were the occurrence of renal colic with the passage of stones twenty years previously, hypertension, said to have been present for at least fifteen years, and nocturia, necessitating passage of urine three to four times a night for many years. He denied having had pains in the bones or extremities, except on two occasions during the past year, when the joints in each first toe became swollen, red and painful.

On examination at the time of his first admission to the hospital the patient was thin and fairly well developed. He appeared chronically ill. A uriferous odor could be detected on his breath. The eyegrounds showed rather marked narrowing and tortuosity of the retinal arteries, but there were no hemorrhages or exudates. Dental caries and pyorrhea were noticeable. No mass could be palpated in the region of the parathyroid glands. The lungs were clear. The heart seemed slightly enlarged to the left. There was an apical systolic murmur of moderate intensity. The second aortic sound was accentuated. The blood pressure, measured in millimeters of mercury, was 190 systolic and 130 diastolic. The radial vessels were rubbery. The abdominal examination gave normal results except for appreciable tenderness in the right costovertebral angle. The remainder of the physical examination added nothing of significance.

Laboratory Data—The Wassermann and Kahn reactions of the blood were negative. Examination of the blood revealed anemia, with a red cell count of 2,600,000 and a hemoglobin concentration of 8.5 Gm. per hundred cubic centimeters (Sahli). The total and differential white cell counts were within normal limits. On repeated examinations the urine showed a specific gravity fixed in the neighborhood of 1.008 and a slight to a moderate trace of albumin. The sediment contained numerous pus cells, an occasional red cell and an occasional granular cast. Four cultures of the urine were sterile. On two occasions the excretion of phthalein was approximately 10 per cent in two hours.

The initial chemical determinations on the serum were as follows: nonprotein nitrogen 78 mg. per hundred cubic centimeters, uric acid 5.5 mg., calcium 7.5 mg., phosphorus 4.1 mg., albumin 4.6 Gm. and globulin 1.6 Gm.

Roentgenograms revealed the following: Mottled areas of increased density were scattered over the regions of both kidneys (fig. 1). There was slight enlargement of the heart in the region of the left ventricle. The long bones and skull revealed considerable general decalcification. No localized cystic areas were observed.

No additional evidence to support a diagnosis of primary hyperparathyroidism could be obtained either in repeated determinations of serum calcium and phosphorus or in studies of urinary calcium, which revealed an excretion of 24 mg. per twenty-four hours during a four day period with the patient on a house diet. Therefore, an exploratory operation for a parathyroid adenoma was deemed inadvisable. The patient was placed on a low protein-low purine diet and was discharged after thirty days of hospitalization. Results of chemical analysis of

the blood at the time the patient was discharged were as follows nonprotein nitrogen 63 mg per hundred cubic centimeters, creatinine 67 mg, uric acid 36 mg, serum calcium 88 mg and serum phosphorus 40 mg

Second Admission—The patient was not seen again until he reentered the hospital in December 1938. His condition had remained stationary for the first several months after discharge. Then increasing weakness, anorexia and loss of weight recurred, with occasional morning nausea and vomiting. Pain and tenderness in the right flank had been present intermittently, but no further attacks of true colic or of hematuria had occurred.

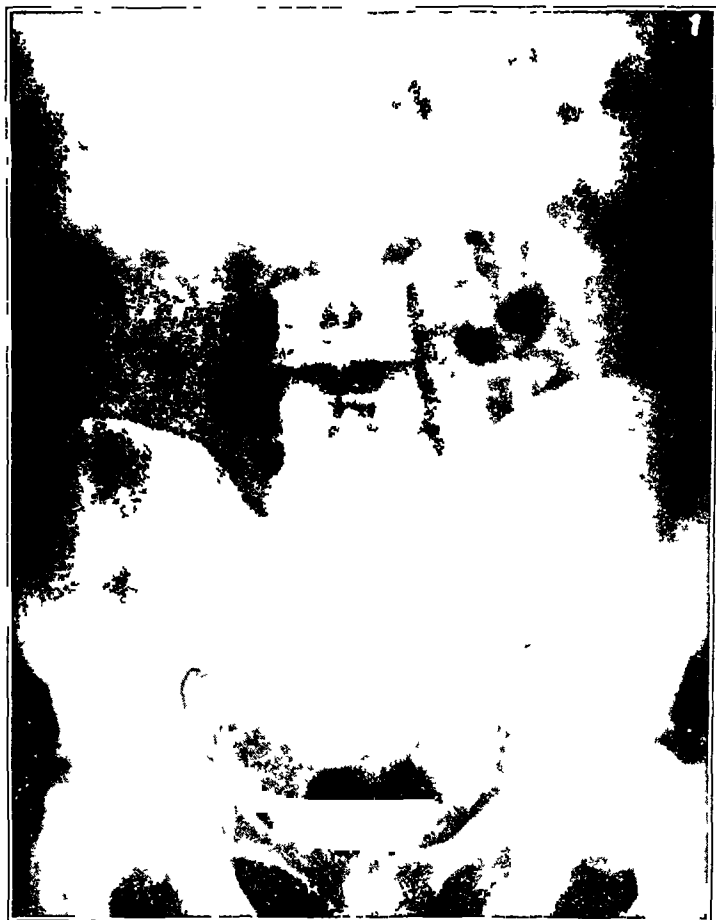


Fig 1—Roentgenogram of the abdomen showing scattered areas of calcification overlying the regions of both kidneys

On entry the patient's rectal temperature was 37.5 C (99.5 F), the pulse rate 90 beats per minute and the respiratory rate 20 per minute. His condition presented the picture of terminal renal insufficiency. He was lethargic, but roused frequently to move about restlessly. Occasional muscular twitchings were visible in the extremities. Chvostek's and Trousseau's signs could not be elicited, however. The skin was dry and pale. There was extreme pallor of the nail beds and the mucous membranes. The breath was strongly urinous. The eyegrounds showed many exudates and both old and recent hemorrhages. There was no papilledema. The other results of the physical examination were essentially the same as those

previously described. The blood pressure measured 160 mm of mercury systolic and 92 mm diastolic.

Anemia was more noticeable, the red cells numbering 1,670,000 per cubic millimeter and the hemoglobin concentration being 60 Gm per hundred cubic centimeters. The white count was 8,700, with neutrophils 83 per cent, lymphocytes 13 per cent, monocytes 3 per cent and basophils 1 per cent. The urine was alkaline, with a specific gravity of 1.007 and a trace of albumin. The sediment contained a few white cells. No red cells or casts were seen. Chemical analysis of the blood showed a nonprotein nitrogen content of 167 mg per hundred cubic centimeters and a creatinine content of 10.2 mg. The serum calcium had fallen to 5.8 mg per hundred cubic centimeters, and the phosphorus had risen to 7.6 mg. The total protein of the serum measured 6.6 Gm, the serum chlorides 557 mg per hundred cubic centimeters, and the plasma carbon dioxide-combining power was 29 volumes per cent.

The patient rapidly lapsed into coma despite parenteral administration of fluids. Muscular twitchings became extreme, and Chvostek's and Trousseau's signs appeared. He died with terminal hyperthermia, the temperature being 41.6 C (107 F).



Fig 2—Parathyroid adenoma with cyst 1 cm in diameter

Necropsy—The examination was performed two hours after death. Description of the gross and microscopic pathologic observations will be limited to the parathyroid glands, the kidneys and the bones. Abnormalities in other organs were essentially those associated with long-standing hypertensive vascular disease.

Parathyroid Glands On the posterior aspect of the right lower pole of the thyroid gland was a small nodular parathyroid containing a cyst 1 cm in diameter (fig 2). The wall of the cyst was 1 mm thick, was pitted on its inner surface and contained a small amount of brown pigment. Three other small brown glands, apparently parathyroids, were found in the customary position.

Histologic examination of the parathyroid gland containing the cyst showed two adenomatous areas of parathyroid tissue separated by connective tissue. These areas were composed mainly of chief cells. Many of the cells were giant forms with large hyperchromatic nuclei (fig 3). Numerous small cystic areas were present, containing desquamated epithelial cells and pink-staining amorphous material. Many small areas of fibrosis were present, and much hemosiderin was to be seen. On one side of the adenoma was a rim of hyperplastic, nonadenomatous parathyroid tissue. This was composed of enlarged, closely packed chief cells with round nuclei and clear cytoplasm (fig 4). Fat cells and cells arranged in cords were almost entirely absent. Sections of the remaining parathyroid resembled in every detail the nonadenomatous tissue just described.

Kidneys The left kidney weighed 100 Gm and the right 120 Gm. They were small and firm. The capsule stripped relatively easily and revealed a nodular surface dotted by numerous small cysts, 2 to 10 mm in diameter, filled with clear brown fluid. The remainder of the surface was made up of numerous firm, raised, rounded gray areas, 1 to 3 mm in diameter, between which small strips of pink renal tissue were visible. The cut surface was pale, mottled gray and pink. The cortex and medulla could not be definitely distinguished. Their combined thickness measured only 7 to 8 mm. A few small red dots could be identified as glomeruli, but the cortical and medullary striations were almost completely obliterated by gray tissue. Scattered through the inner two thirds of the parenchyma

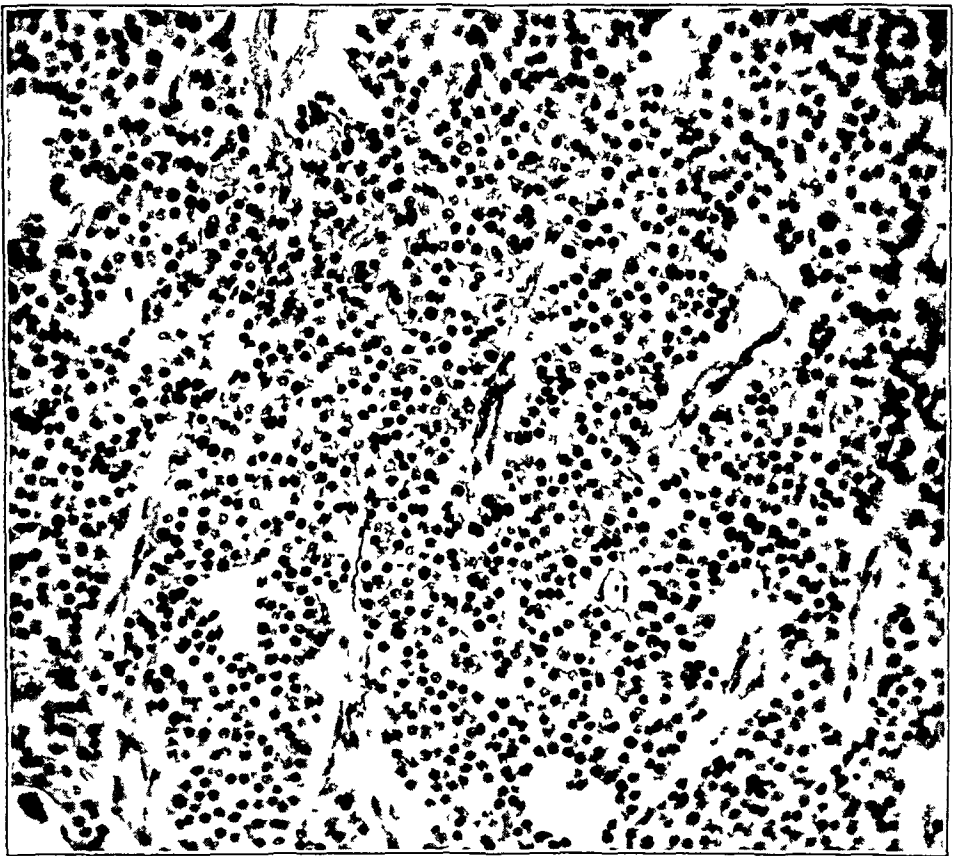


Fig 3—Photomicrograph of parathyroid adenoma. Note the large hyperchromatic nuclei scattered among chief cells. Blood vessels are numerous. $\times 210$

were numerous tiny orange streaks and dots which felt gritty on palpation. The pyramids appeared flattened and deformed. Small renal arterioles stood patent above the cut surface. Peripelvic fat was considerably increased. The pelvis of the left kidney appeared slightly enlarged and was lined by smooth, gray mucosa. The left ureter was of usual caliber, and its mucosal surface was intact. There was a localized area of dilatation of the right ureter, measuring 2 to 3 cm in length, just at the pelvic brim. No cause for this was apparent. No calculi were found on either side. An unusual formation in the left renal artery was a dissecting aneurysm of the wall extending for a distance of 2 cm just proximal to the kidney.

Microscopic examination of the kidneys revealed that most of the glomeruli were hyalinized or had extremely thickened Bowman's capsules. The few remaining glomeruli showed enlarged capillary tufts. Many of the tubules were dilated and contained pink-staining amorphous material, giving in some areas an appearance not unlike that of the thyroid gland. There were numerous calcified areas scattered throughout the sections, chiefly in and around the tubules. The interstitial tissue was appreciably increased and was infiltrated with round cells in numerous areas. The arterioles showed great thickening of the intima. Several large cysts lined by low cuboidal epithelium were present.

Bones The bone structures did not appear grossly abnormal. The vertebral and costal marrow was red and cellular, the femoral marrow, fatty. Microscopically there was little evidence of resorption or regeneration of bone. Along the bony

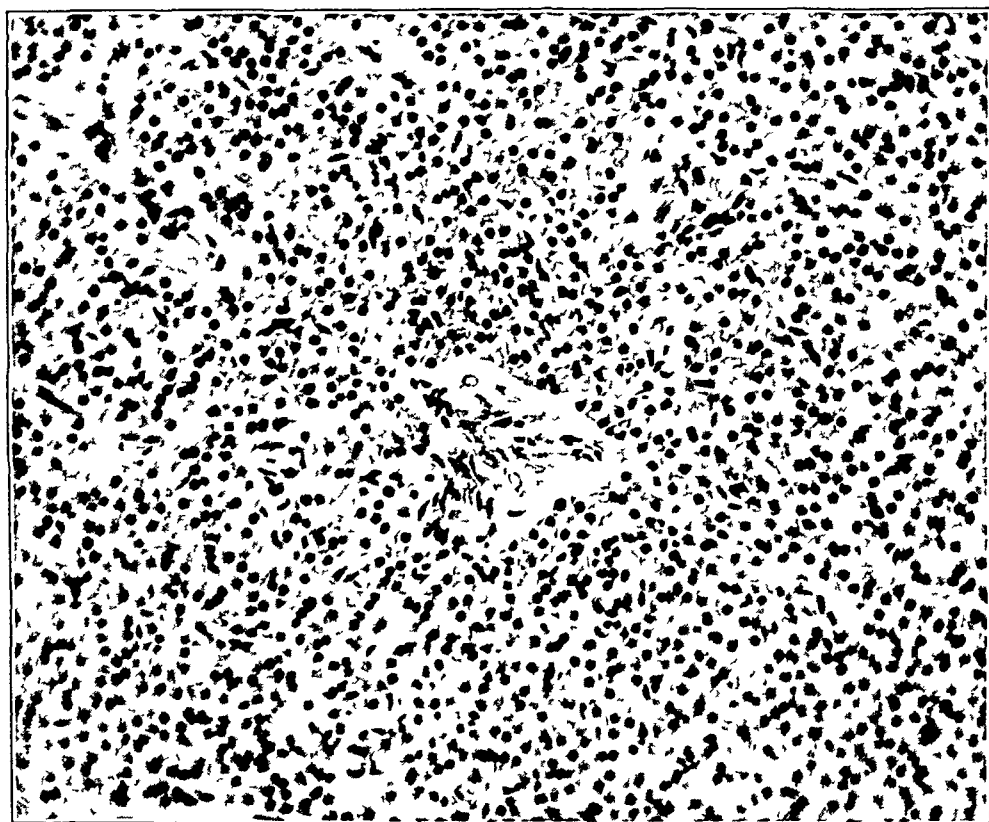


Fig 4—Photomicrograph of a hyperplastic nonadenomatous parathyroid gland. Note the compactness of cells, absence of fat cells and absence of distinct cords of cells. $\times 210$

spicules in some areas strands of loosely arranged connective tissue were seen, while in others the spicules appeared hollowed out and filled with fibrous tissue.

COMMENT

An unusual clinical feature of this case was, on the one hand, the roentgenogram of the abdomen showing finely mottled areas of density over the regions of both kidneys, which were suggestive of hyperparathyroidism. In view of the past history of renal colic and the sterile cultures of the urine, this renal calcinosis could not be satisfactorily

explained on any basis other than hyperparathyroidism. On the other hand, the decreased calcium and the elevated inorganic phosphorus of the serum and the low calcium excretion in the urine were not consistent with this diagnosis and at first appeared to exclude it. However, it was suggested that the atypical chemical abnormalities could be explained by the effect of prolonged renal insufficiency acting as a complication of primary hyperparathyroidism.

After the autopsy, the evolution of the patient's disease could be reconstructed with more certainty. The presence of a definite parathyroid adenoma left no doubt that the patient did have hyperparathyroidism. That this was the sole cause of the renal disease cannot be stated positively, but it seems likely that it was. Long-continued renal insufficiency gradually resulted in the retention of phosphates, and this in turn led to hypocalcemia in spite of the presumably increased amount of parathyroid hormone in the blood due to the tumor. Thus the paradoxical situation arose in which hyperparathyroidism was indirectly the cause of hypocalcemia, and even tetany, in the terminal stage.

Nevertheless, it was also apparent from the observations made at autopsy that the parathyroid glands as a whole were attempting to combat this tendency toward tetany and the increasing retention of phosphates. The parathyroid hyperplasia in the nonadenomatous glands was exactly similar to that seen in man in chronic renal insufficiency^{2b} and to that produced in the experimental animal by repeated injections of phosphates.⁴ Hence, if the parathyroid tumor had been removed when the patient first came to us, the remaining glands would have had the whole burden of trying to regulate the calcium and phosphorus content of the serum, and the patient would undoubtedly have died much sooner.

SUMMARY

A case with the following outstanding features is reported: (1) hyperparathyroidism due to a parathyroid adenoma, (2) diffuse renal calcinosis and renal insufficiency, (3) values for serum calcium and inorganic phosphorus of 5.8 and 7.6 mg, respectively, per hundred cubic centimeters shortly before death, and (4) secondary hyperplasia of the three nonadenomatous parathyroid glands.

Dr. Fuller Albright made valuable suggestions in the preparation of this paper, and Dr. Benjamin Castleman studied the histologic sections of the parathyroid glands.

4. Drake, T. G., Albright, F., and Castleman, B. Parathyroid Hyperplasia in Rabbits Produced by Parenteral Phosphate Administration, *J. Clin. Investigation* **16**: 203-206, 1937.

DIASTATIC ACTIVITY OF HUMAN BLOOD

MICHAEL SOMOGYI, PH D

ST LOUIS

The presence of diastase¹ in human blood was first noted in 1846² and subsequently the enzyme was found to be a normal constituent of mammalian blood in general. In 1863 the enzyme was shown to be present also in urine, and its origin was traced to the blood³. Eventually diastase was detected in lymph,⁴ in pericardial fluid^{1b} and in feces⁵. Hepatic bile is almost completely devoid of diastase,⁶ but the enzyme can be detected in the bile when the diastase content of blood is greatly increased by ligation of the pancreatic ducts⁷. Bile from the common bile duct and the gallbladder may contain appreciable amounts of diastase as the result of pancreatic reflux⁸. Assertions that measurable amounts of diastase are present in the cerebrospinal fluid,⁹ the liver and the kidneys¹⁰ are open to doubt. In this laboratory it was not possible to detect diastase in the cerebrospinal fluid of normal persons. Again,

From the laboratory of the Jewish Hospital

1 The terms diastase and amylase are often used interchangeably. I prefer the term diastase to denote the enzyme dealt with in this study, an enzyme which is not only an amylase, but a glycogenase and a dextrinase as well.

2 Magendie. Note sur la présence normale du sucre dans le sang. *Compt Rend Acad d sc* **23** 189, 1846.

3 Cohnheim, J. Zur Kenntnis der zuckerbildenden Fermente, *Virchows Arch f path Anat* **28** 241, 1863.

4 (a) Rohmann. Zur Kenntnis des diastatischen Ferments der Lymph, *Arch f d ges Physiol* **52** 157, 1892. (b) Carlson, A. J., and Luckhardt, A. B. On the Diastases in the Blood and the Body Fluids, *Am J Physiol* **23** 148, 1908.

5 (a) Brown, T. R. The Normal Amount of Diastatic Ferment in the Feces and Its Variation in Certain Diseases of the Pancreas and in Achylia Gastrica, *Bull Johns Hopkins Hosp* **25** 200, 1914. (b) McClure, C. W., and Pratt, J. H. A Study of the Diastatic Activity of Urine and Feces, with Special Reference to Diseases of the Pancreas, *Arch Int Med* **19** 568 (April) 1917.

6 Popper, H. L. Pankreassaft in den Gallenwegen, *Arch f klin Chir* **175** 660, 1933.

7 Zucker, T. F., Newburger, P. G., and Berg, B. N. The Amylase of Serum in Relation to Functional States of the Pancreas, *Am J Physiol* **102** 209, 1932.

8 Colp, R., and Doubilet, H. The Clinical Significance of Pancreatic Reflux, *Ann Surg* **108** 243, 1938. The Operative Incidence of Pancreatic Reflux in Cholelithiasis, *Surgery* **4** 837, 1938. Popper⁶.

9 (a) Kasahara, M., and Takashi, S. Studien über Liquor cerebrospinalis, *Ztschr f d ges exper Med* **74** 702, 1930. (b) Carlson and Luckhardt^{4b}.

10 Borchardt, L. Ueber das zuckerbildende Ferment der Leber, *Arch f d ges Physiol* **100** 259, 1903.

while Kuttner and I¹¹ have found substantial amounts of diastase in human milk, reports on the presence of diastase in cow's milk¹² could not be confirmed. Accumulating experimental data also indicate that hepatic cells contain no diastase, the amount of enzyme that can be extracted from liver is so small that it is probably all derived from the intercellular fluid.

Reports concerning the character of blood diastase (as reflected in the chemical nature of the reducing sugars it produces from starch), its origin or source, its possible functions and its changes in pathologic conditions are replete with contradictions. On the basis of careful scrutiny of the experimental technic employed by various investigators, and in the light of studies which my collaborators and I have made, I feel that the mass of conflicting results is mainly due to deficient analytic and experimental procedures. The quantitative assay of any enzyme presents difficulties not usually encountered in ordinary chemical analyses. Diastase offers more complexities than most other enzymes, a fact which is not surprising if one realizes that even the identification of the products from the diastatic reaction has remained uncertain to date, despite the extensive work of a large number of investigators who devoted much of their efforts to the subject. Little wonder it is, then, that clinical investigators were unaware of the difficulties that are inherent in the quantitative estimation of diastase. A systematic and critical survey of the problem should be helpful in providing a background for a more judicious clinical application of studies on diastase.

NATURE OF BLOOD DIASTASE

It has been asserted that blood diastase differs from salivary and pancreatic diastase¹³. This opinion was based on observations that the reducing substances produced from starch differed according to the source of the enzyme. Experiments in this laboratory have definitely demonstrated that the split products of starch are identical, whether the diastase employed is derived from the blood, from the salivary glands or from the pancreas. These split products are mixtures of three kinds of reducing substances, namely, maltose, dextrose and nonfermentable reducing matter, the last representing a series of dextrans. My studies¹⁴ dealing with the kinetic aspects of diastatic reactions disclosed

11 Kuttner, M., and Somogyi, M. Diastase in Milk, *Proc Soc Exper Biol & Med* **32** 564, 1934.

12 Chrzascz, T., and Goralowna, C. Milchdiastase und ihre Eigenschaften, *Biochem Ztschr* **166** 172, 1925.

13 Hamburger, C. Vergleichende Untersuchung über die Einwirkung des Speichels, des Pankreas- und Darmsaftes sowie des Blutes auf Starkekleister, *Arch f d ges Physiol* **60** 543, 1895. Borchardt¹⁰

14 Somogyi, M. Interpretation of the Saccharogenic Action of Diastase on the Basis of Substrate Competition, *J Biol Chem* **134** 301, 1940.

the fact that, depending on such experimental conditions as the duration of the reaction and the relative concentrations of the enzyme and the substrate, the same enzyme preparation may produce in one instance only nonfermentable reducing matter (dextrins), in another dextrins and maltose and in still another a combination of these substances with dextrose. These facts eluded observation by previous workers mainly because analytic methods for the quantitative estimation of each of the saccharides in mixtures of them¹⁵ were not available.

SOURCES OF BLOOD DIASTASE

Since the salivary and pancreatic glands produce large quantities of diastase, earlier investigators assumed a priori that these organs were sources of blood diastase.

Salivary Glands—A review of the literature indicates that normally blood diastase does not originate either directly or indirectly in the salivary glands. Extirpation of the salivary glands of various animals resulted in no appreciable diminution of the diastatic activity of the blood¹⁶. But it would hardly be sound to conclude from this that the salivary glands can be excluded with certainty as a source of diastase, since the anatomic exigencies seem to preclude a complete extirpation of these glands. There are some animals, however, in which the salivary glands produce no diastase, but in which there is, nevertheless, a high diastatic activity of the blood¹⁷. Such an animal is the dog, whose blood contains from ten to twenty times as much diastase as does human blood.

In certain pathologic changes of the salivary duct system, however, increases in blood diastase have been demonstrated. Ligation of the parotid ducts has been shown to increase the diastase content of blood¹⁸. In acute inflammatory occlusion or suppurative lesions of the salivary duct system there is usually an increased level of diastatic activity¹⁹. This is probably due to diffusion of the enzyme into the blood stream after the cell membranes of the acinic tissue have been damaged.

15 Somogyi, M. Analysis of Diastatic Split Products of Starch, *J Biol Chem* **102** 179, 1938.

16 Schlesinger, W. Ueber den Ursprung des diastatischen Fermentes im Blute und über seine Beziehungen zum Diabetes mellitus, *Deutsche med Wchnschr* **34** 593, 1908.

17 King, C. E. Studies on Blood and Urinary Amylase, *Am J Physiol* **35** 301, 1914.

18 Polacco, E., and Midana, A. Influenza della ligatura dei dotti parotidei sulla amilasi del sangue e dell'urina in cani spancreatici e non, *Arch ed atti d Soc. ital di chir* **35** 654, 1929.

19 (a) Dunlop, G. A. The Diastatic Index in Acute Parotitis, *Lancet* **2** 183, 1933. (b) Branisteanu, D., and Boutroux, A. Contribution à l'étude de l'élimination de l'amylase urinaire dans divers cas normaux et pathologiques, *Arch d mal de l'app digestif* **23** 746, 1933.

Pancreas—An enormous amount of experimental work has been performed to determine the part the pancreas plays as a source of blood diastase. While the results have not been uniform, and in many cases have been quite contradictory, they permit the unqualified conclusion that under normal conditions the pancreas is not a source of blood diastase. Complete extirpation of the pancreas, although not an easy procedure, is anatomically feasible in some experimental animals. The majority of investigators²⁰ reported a fall in the level of blood diastase soon after pancreatectomy, but this fall was always temporary. The maximum fall occurred about the third postoperative day and was followed by an approximate,²¹ or even complete,²² reversion to the normal level. A few investigators found no changes at all, others observed slight elevations of the blood diastase.²³ It is significant that not a single investigator has reported the disappearance or even an appreciable diminution of blood diastase following pancreatectomy.

20 (a) Bambridge, F. A., and Beddard, A. P. The Diastatic Ferment in the Tissues in Diabetes Mellitus, *Biochem J* **2** 89, 1907. (b) Otten, H., and Galloway, T. C. The Relation of the Pancreas to the Blood Diastases in the Dog, *Am J Physiol* **26** 347, 1910. (c) Gould, L. K., and Carlson, A. J. Further Studies on the Relation of the Pancreas to Serum and Lymph Diastases, *ibid* **29** 165, 1911. (d) Van der Erve, J. On the Rôle of the Kidneys in the Regulation of the Concentration of the Serum Diastase, *ibid* **29** 182, 1911. (e) Davis, L. H., and Ross, E. L. The Sources of Diastases of the Blood, *ibid* **56** 22, 1921. (f) Brill, I. C. Studies in the Diastatic Activity of the Blood, with a Consideration of Its Value in Clinical Diagnosis, *Arch Int Med* **34** 542 (Oct) 1924. (g) Crandall, L. A., and Cherry, I. S. The Regulation of Blood Lipase and Diastase by the Liver, *Am J Physiol* **97** 515, 1931. (h) Reid, E., Quigley, J. P., and Myers, V. C. Studies on Animal Diastases. V. Blood and Tissue Diastases with Special Reference to the Depancreatized Dog, *J Biol Chem* **99** 615, 1933. (i) McCaughan, J. M. The Value of Estimations of the Amylase of the Blood in the Diagnosis of Suspected Pancreatic Disease, *Surg, Gynec & Obst* **59** 598, 1934. (j) Friedman, I., and Thompson, W. R. Induced and Spontaneous Changes in Blood Amylase Particularly in Relationship to the Pancreas, *Ann Surg* **104** 388, 1936. (k) Rachmilewitz, M. Clinical Significance of Blood Diastase in Disease of the Liver and Bile Ducts, *Harefuah* **12** 111, 1937. (l) Branch, C. D., and Zollinger, R. The Value of Blood Diastase in the Diagnosis of Common Duct Stone, *Am J Surg* **41** 233, 1938. (m) Schlesinger¹⁶. (n) King¹⁷.

21 Otten and Galloway^{20b}. Gould and Carlson^{20c}. Van der Erve^{20d}.

22 Schlesinger¹⁶. Brill^{20f}. Reid, Quigley and Myers^{20h}. McCaughan²⁰ⁱ. Rachmilewitz^{20k}. Branch and Zollinger^{20l}.

23 (a) Milne, L. S., and Peters, H. Observations of the Glycolytic Power of the Blood and Tissues in Normal and Diabetic Conditions, *J Metab Research* **26** 415, 1912. (b) Karsner, H. T., Koeckert, H. L., and Wohl, S. A. The Diastatic Activity of the Blood in Experimental Hyperglycemia, *J Exper Med* **34** 349, 1921. (c) Cammidge, P. J., Forsyth, J. A. C., and Howard, H. A. H. The Blood and Urine in Pancreatic Disease, *Lancet* **2** 393, 1920. (d) Reid, C., and Narayana, B. Studies in Blood Diastase, *Quart J Exper Physiol* **20** 305, 1930. (e) Golden, L. A., Sieracki, L. A., Handelsman, M. B., and Pratt, J. H. Diastatic Activity of Blood and Urine When the Pancreatic Ducts Are Permanently Closed, *Am J Digest Dis* **6** 327, 1939. (f) Carlson and Luckhardt^{4b}.

Some workers were inclined to interpret the temporary drop after pancreatectomy as a proof that the pancreas is at least a partial contributor to the blood diastase. But if this were true, one would expect a continuous drop in the diastase level rather than a restoration to the preoperative level. Gradual compensation by the salivary glands is out of the question in the case of the dog, the animal generally used in these experiments. The suggestion that blood diastase may be supplied after pancreatectomy from reserve pancreatic diastase stored in the tissues²⁴ has no foundation in either experimental evidence or logical reasoning. If storage of pancreatic enzymes in tissues were to occur, trypsin and lipase would also be accumulated, with calamitous effects on body tissues.

The transient drop following pancreatectomy need not be attributed to the absence of the gland, since other operative procedures of even less magnitude exert a similar effect on blood diastase.²⁵ A significant fact to which I wish to direct attention is that ketosis almost inevitably sets in during the first few days after operation and persists until the diabetic condition of the animals is adequately controlled. Ketosis in human beings invariably entails a substantial lowering of the blood diastase²⁵ and a similar effect is the most plausible cause of the transient drop in depancreatized dogs. After the first few postoperative days, when ketosis is checked by diet and insulin, the blood diastase is restored to the preoperative level, provided that no complications follow the operation. It is likely that in those experiments in which restoration to the preoperative level did not occur,²⁶ the diabetes was not adequately controlled, and persistent ketosis was responsible for the continued depression of the diastase level. In those cases, on the other hand, in which the diastase content of the blood showed not even a transitory drop, it is likely that the diabetes caused by the operation was skilfully controlled from the outset.

While the evidence is quite conclusive that the pancreatic diastase under normal physiologic conditions bears no relation to the blood diastase, there is no doubt that acute diseases of the pancreas, whether induced experimentally or observed clinically, do cause an increase in the diastase content of the blood. Traumas induced experimentally by various means have resulted in great increases of diastatic activity, the extent of the rise usually being proportional to the degree of injury.²⁷

24 Lewis, D. S., and Mason, F. H. The Diastatic Ferments of the Blood, *J. Biol. Chem.* **44** 455, 1920. Zucker, Newburger and Berg.⁷ Schlesinger.¹⁶

25 Gray, S. H., Probstein, J. G., and Heffetz, C. J. Clinical Studies on Blood Diastase. I. Low Blood Diastase as an Index of Impaired Liver Function, *Arch. Int. Med.*, to be published.

26 Zucker, Newburger and Berg.⁷ Friedman and Thompson.^{20j}

27 Wohlgemuth, J., and Noguchi, Y. Experimentelle Beiträge zur Diagnostik der subcutanen Pankreasverletzungen, *Berl. klin. Wchnschr.* **49** 1069, 1912. McClure and Pratt.^{5b} Zucker, Newburger and Berg.⁷ King.¹⁷ McCaughan.²⁰ⁱ

Lesions of the pancreas similar to those found in acute pancreatitis have been produced experimentally by injection of bile, bile salts, bacterial suspensions and irritative chemicals into the pancreatic ducts,²⁸ determinations of diastase made during such experiments have always given elevated values. The results obtained by ligation of the pancreatic ducts are fairly uniform in that nearly all workers²⁹ reported a rapid rise in the diastatic level within twenty-four hours, a maximum being reached in about three days, after which a gradual drop and return to the normal level were observed.

The changes in blood diastase that are associated with these pancreatic lesions can be readily understood. Trauma of the pancreas disrupts mechanically the acinar membranes and allows diffusion of diastase (as well as of lipase and trypsin) into the interstitial fluid, whence it is absorbed into the blood.²⁰ⁱ The rise that follows ligation of the pancreatic ducts is due to backing-up and absorption of enzymes into the blood, while the subsequent fall is due to the cessation of functions of the secreting cells, atrophy following in the wake of injury.³⁰ In spite of the atrophy the blood diastase is maintained indefinitely at the normal level, a fact which reinforces the view that the pancreas cannot be the source of normal blood diastase.

Still another mechanism for the ingress of pancreatic diastase into the blood has been suggested.³¹ The subcutaneous injection of acetyl- β -methylcholine hydrochloride in dogs causes a sharp rise in the blood diastase. After pancreatectomy this rise does not occur. Since acetyl- β -methylcholine supposedly produces spastic closure of the pancreatic duct by its action on the parasympathetic nervous system, it is assumed that

28 (a) Archibald, E. The Experimental Production of Pancreatitis in Animals as the Result of the Resistance of the Common Duct Sphincter, *Surg, Gynec & Obst* **28** 529, 1919. (b) Clasen, A. C., Johnstone, P. N., and Orr, T. G. Blood Amylase in Experimental Pancreatitis, *ibid* **59** 756, 1934. (c) Antopol, W., Schiffrin, A., and Tuchman, L. Blood Amylase Response to Acetylcholine and Its Modification by Physostigmine and Atropine, *Proc Soc Exper Biol & Med* **32** 383, 1934. (d) Branisteanu and Boutroux^{19b}. (e) McCaughan²⁰ⁱ.

29 (a) Clerc, A., and Loeper, M. Influence de la ligature du canal pancreatique sur le pouvoir amylolytique du sang, *Compt rend Soc de biol* **66** 871, 1909. (b) Elman, R. The Variations of Blood Amylase During Acute Transient Disease of the Pancreas, *Ann Surg* **105** 379, 1937. (c) Johnson, C. E., and Wies, C. H. Influence of Ligation of Pancreatic Ducts of Dogs upon Serum Amylase Concentration, *J Exper Med* **55** 505, 1932. (d) Zucker, Newburger and Berg.⁷ (e) Kasahara and Takashi.^{9a} (f) King.¹⁷ (g) Gould and Carlson.²⁰ⁱ (h) McCaughan.²⁰ⁱ (i) Friedman and Thompson.^{20j} (j) Branch and Zollinger.²⁰ⁱ

30 Gray, S. H., Probst, J. G., and Heifetz, C. J. Transient Acute Pancreatitis, *Ann Surg* **108** 1029, 1938. Gould and Carlson.^{20c} McCaughan.²⁰ⁱ Friedman and Thompson.^{20j} Clasen, Johnstone and Orr.^{28b} Clerc and Loeper.^{29a}

31 Friedman and Thompson.^{20j} Antopol, Schiffrin and Tuchman.^{28c}

some such nerve mechanism may play a part in the production of acute pancreatic lesions and in the precipitation of the clinical condition denoted as transient acute pancreatitis

Intestinal Resorption of Salivary and Pancreatic Diastase—The suggestion that the secreted pancreatic diastase is resorbed from the intestinal tract into the blood stream³² is hardly acceptable in view of the size and the protein nature of the enzyme molecule. As a matter of fact, direct experimental evidence invalidates this hypothesis. When large amounts of diastase were introduced into the intestine of experimental animals, the diastase content of the blood showed no rise,⁷ and, conversely, no drop resulted from experimental pancreatic fistulas in dogs³³ and accidental pancreatic fistulas in man.³¹

Liver—The liver has been considered another possible source of blood diastase.³⁵ It has been assumed that the liver contains large quantities of the enzyme, required for the saccharification of glycogen when it becomes necessary to supply dextrose to the blood.³⁶ All available experimental evidence is contrary to this assumption. In the first place, I have never been able, by any method, to extract diastase from the liver in quantities greater than would correspond to the enzyme content of the extracellular fluid present in the tissues. In other words, the diastase obtainable from a gram of liver is only a fraction of the diastase contained in a gram of plasma. Second, analysis of the carbohydrates present in hepatic tissues shows only the presence of glycogen and dextrose and never a trace of maltose or nonfermentable reducing substances, although both the latter are invariably present among the split products formed by diastasis of starch and glycogen.³⁷ On the basis of these observations, I have reason to assume that hepatic cells contain no diastase at all. This is strongly supported by recent experiments demon-

32 Cohen, I. Variations in Blood and Urine Diastase Content in Relation to Meals, *Brit J Exper Path* **6** 173, 1925. Crandall and Cherry^{20g}

33 (a) Elman, R., and McCaughan, J. M. The Quantitative Determination of Blood Amylase with the Viscosometer, *Arch Int Med* **40** 58 (July) 1927.
(b) Zucker, Newburger and Berg.⁷

34 Henning, N., and Bach, E. Untersuchungen über die Resorption diastatischer Fermente im menschlichen Darm, *Deutsches Arch f klin Med* **168** 374, 1930.

35 Rachmilewitz, M. Blood Diastase in Hepatic and Biliary Disease, *Am J Digest Dis* **5** 184, 1938. Cajori, F. A., and Vars, H. M. The Effect of Chloroform Anesthesia on the Serum Amylase and Liver Esterase, *Am J Physiol* **124** 149, 1938. King.¹⁷ Gould and Carlson.^{20c} Rachmilewitz.^{20h} Cammidge, Forsyth and Howard.^{23c}

36 Cohen, S. J. Studies in Blood Diastases, *Am J Physiol* **69** 125, 1924. Reid, E., and Myers, V. C. Studies on Animal Diastases. IV. The Effect of Insulin on the Diastatic Activity of the Blood in Diabetes, *J Biol Chem* **99** 607, 1933. Reid, Quigley and Myers.^{20h} Reid and Narayana.^{23d}

37 Somogyi, M. Unpublished data.

stating that glycogenolysis in the liver is effected by an enzyme system that has nothing in common with diastase. Cori and associates have shown that in the process of hepatic glycogenolysis, glycogen is split directly to hexose phosphate, which then is dephosphorylated by a phosphatase to the state of free dextrose,³⁸ diastase having no part whatever in the process. In the face of these observations, the reports concerning the role of blood diastase in glycogenolysis are without foundation. Similarly, experiments have failed to demonstrate any relation between the diastase and the sugar content of the blood.³⁹

Other Sources—No evidence has been brought forward designating any other organ as the site of diastase formation. Skeletal muscle might be considered as a possible source, but thus far has not been adequately studied. In my analysis of muscle tissues I failed to detect the characteristic split products that are formed by diastase,³⁷ but this negative observation in itself cannot serve as the basis for any definite conclusion.

FUNCTION OF BLOOD DIASTASE

It is a generally accepted view that diastase in the blood is a waste product on its way to excretion in the urine. This seems scarcely acceptable in the light of the fact that while dog's blood contains ten to thirty times as much diastase as normal human blood, the enzyme appears in the dog's urine only when it reaches the highest levels in the blood.

Another pertinent fact is that human milk (but not cow's milk!) contains fifty times as much diastase as does blood, yet this amount of enzyme has no physiologic function that one can think of. One would hesitate, however, to regard milk, on this basis, as a vehicle for waste material.

In view of these two facts, I feel that at present the role of diastase in blood is as obscure as is its origin.

METHODS FOR ESTIMATION OF DIASTASE

Since the reliability of the analytic methods is of pivotal importance in any experimental investigation, it is in order to scrutinize briefly the methods employed for the quantitative estimation of blood diastase. These are mainly of three types:

38. Cori, G. T., Colowick, S. P., and Cori, C. F. The Enzymatic Conversion of Glucose-1-Phosphoric Ester to 6-Ester in Tissue Extracts, *J. Biol. Chem.* **124**: 543, 1938.

39. (a) Zoepffel, H. Das akute Pankreasodem, eine Vorstufe der akuten Pankreasnekrose, *Deutsche Ztschr. f. Chir.* **175**: 301, 1922. (b) Harrison, G. A., and Lawrence, R. D. Diastase in Blood and Urine as a Measure of Renal Efficiency, *Lancet* **1**: 169, 1923. (c) Markowitz, J., and Hough, H. B. A Study of Blood Diastases in Depancreatized Dogs, *Am. J. Physiol.* **75**: 571, 1926. (d) Otten and Galloway.^{20b} (e) Karsner, Koeckert and Wohl.^{23b}

One group of methods is based on the measurement of the starch-splitting (amylolytic) action of diastase, the action by which starch is depolymerized until it no longer gives a blue color with iodine. A method of this type, most widely used both in Europe and in America, is that of Wohlgemuth⁴⁰. Careful analysis of Wohlgemuth's publications and my own considerable experience with the method indicate that it does not permit measurement of relatively small changes and it does not make possible accurate determinations of values appreciably below the normal. A basic shortcoming of this technic is the lack of adequate standardization. This is the likely explanation of the fact that the method was modified in one way or another by almost all investigators who used it, most of the modifications resulting in corruption rather than improvement of the original procedure. At the same time, I find that the results obtained with the method by Wohlgemuth himself are, on the whole, fairly accurate and reliable. Apparently, he failed to describe some details of the technic which he, perhaps automatically, followed. The inability of other workers to use the method correctly, however, led to the most confusing array of results, such as the finding of diastase in cow's milk and in the spinal fluid of healthy human beings, neither of which substances normally contains any of the enzyme. In this laboratory the method of Wohlgemuth, with certain precautions and standardizations, yielded results which, within certain limits, were comparable with those obtained by methods developed here⁴¹. With these precautions, however, Wohlgemuth's method became too tedious and time consuming.

A second group of methods is based on the measurement of changes in the viscosity of starch paste under the action of diastase⁴². The inadequacy of such methods has been discussed in another paper⁴³.

The third group of methods is based on the measurement of reducing sugars formed by diastatic hydrolysis. In these methods, as exemplified by the method of Myers and Killian,⁴⁴ the standard conditions were arbitrarily picked with complete disregard to the kinetic aspects of the reaction. This, of necessity, again led to endless confusion, as

40 Wohlgemuth, J. Ueber eine neue Methode zur quantitativen Bestimmung des diastatischen Ferments, *Biochem Ztschr* **9** 1, 1908.

41 Steinberg, F. Comparative Determinations of Blood Diastase by Several Methods, to be published.

42 Davison, W. C. A Viscosometric Method for the Quantitative Determination of Amylase, *Bull Johns Hopkins Hosp* **37** 281, 1935.

43 Somogyi, M. Micromethods for the Estimation of Diastase, *J Biol Chem* **125** 399, 1938.

44 Myers, V. C., and Killian, J. A. Studies on Animal Diastases. I. The Increased Diastatic Activity of the Blood in Diabetes and Nephritis, *J Biol Chem* **29** 179, 1917.

illustrated by reports which indicated a yield of reducing sugars, computed as maltose, greater than could possibly be obtained if all of the available starch had been split into maltose. These reports were made in the face of the well known fact that only a maximum of about 85 per cent of the available starch can be converted by diastatic action into "maltose."

It has been asserted that the measurement of either the starch-splitting (amylolytic) or the sugar-producing (saccharogenic) activity furnishes an inaccurate index of the enzyme action, because only one phase of the reaction is considered in either procedure⁴⁵. Thus, it was held that there was no real direct parallelism between these two activities. Extensive studies in this laboratory and those in others⁴⁶ on the two phases of the reaction indicated that there are conditions under which the amylolytic and the saccharogenic phase show complete parallelism.

The two methods in use in this laboratory belong to the first and third groups of methods⁴³. They are based on an extensive study of the kinetic principles of the reaction of diastase with starch. To express the diastatic activity of a given medium, the amount of reducing sugars it produces from starch under precisely standardized conditions is stated. Thus, in the instance of blood serum (or plasma) a diastatic activity of, for example, 120 means that under the prescribed standard conditions 100 cc of the serum produces, from starch, cleavage products which have the same copper-reducing power as 120 mg of dextrose.

This, I feel, is for the present the simplest and most logical quantitative expression of diastatic activity. The great variety of enzyme "units" used in other methods are of such arbitrary construction that it is impossible to bring to a common denominator, to correlate and mutually to check results obtained by different methods.

In my rapid method, which is based on the amylolytic activity of the enzyme, it is the reaction time that is the object of quantitative measurement and not the reducing power of the reaction products. But the results obtained by this procedure are readily computable in terms of reducing power and are identical with the results obtained with my other method, in which the reducing power is the quantity actually determined. Either of the two procedures permits for the first time the accurate estimation of low values of diastatic activity, while estimated

45 Elman, R., Arneson, N., and Graham, E. A. Value of Blood Amylase Estimations in the Diagnosis of Pancreatic Disease, *Arch Surg* **19** 943 (Dec, pt 1) 1929.

46 Johnson, W. A. A Proposed Method for the Routine Valuation of Diastase Preparations, *J Am Chem Soc* **30** 798, 1908. Sherman, H. C., Kendall, E. C., and Clark, E. D. Studies on Amylases. I. An Examination of Methods for the Determination of Diastatic Power, *ibid* **32** 1073, 1910.

values are equally accurate in the high ranges. Simplicity and rapidity of execution make the procedures, especially the one based on amylolytic activity, readily available for clinical use.

DIASTATIC ACTIVITY OF NORMAL HUMAN BLOOD

The variations in the diastatic activity of the blood of different persons are considerable, amounting to as much as 200 per cent.⁴⁷ This fact makes it somewhat difficult to draw a sharp line of demarcation between normal and pathologic values, especially in the subnormal ranges. But if the normal level for a given person is known, even moderate changes are significant, for the diastase content of the blood in any healthy person is maintained at a fairly constant level.⁴⁸

In order to determine the normal range of variations, I performed estimations of the diastatic activity of the blood plasma on a group of 170 young and middle-aged adults, chiefly interns, nurses and members of the visiting staff, all persons without any known or suspected disease. The results are shown in figure 1. It can be seen that 80.5 per cent of these values are found to be within the limits of 80 and 150, the remaining 19.5 per cent falling partly in the low range, between 60 and 80, and partly in the high range, between 150 and 180. Basing the decision on these results and on a large number of clinical observations, I have adopted 80 to 150 as the range of normal diastatic activity of human blood plasma. Diastatic activities between 60 and 80 and between 150 and 180 are considered as borderline values.

A second, larger group of "normal" persons included 1,209 hospital patients who suffered from no condition which, so far as I was aware, was likely to alter the diastase level. All patients with any possible involvement of the biliary tract, pancreas, kidneys, heart or thyroid were excluded because of the possible effect of the disease on the diastase

47 (a) Benczur, J. V. Beitrag zur klinischen Verwertbarkeit der Diastase-menge in Blutserum und Urin, *Wien klin Wchnschr* **23**:890, 1910. (b) Stocks, P. The Quantitative Determination of Amylase in Blood Serum and Urine as an Aid to Diagnosis, *Quart J Med* **9**:216, 1916. (c) Lavaglio, R. L'indice diastatico del sangue e delle urine in un gruppo di epatopazienti, *Policlinico (sez med)* **35**:221, 1928. (d) Somogyi, M. Blood Diastase as an Indicator of Liver Function, *Proc Soc Exper Biol & Med* **32**:538, 1934. (e) Gray, S. H., and Somogyi, M. Relationship Between Blood Amylase and Urinary Amylase in Man, *ibid* **36**:253, 1937. (f) Cole, W. H. Acute Pancreatitis, with Special Reference to Pathogenesis and the Diagnostic Value of the Blood Amylase Test, *Am J Surg* **40**:245, 1938. (g) Lewis and Mason²⁴. (h) Cohen³². (i) Harrison and Lawrence^{39b}. (j) Elman, Arneson and Graham⁴⁵.

48 McCaughan²⁰¹. Cohen³². Harrison and Lawrence^{39b}. Stocks^{47b}. Lavaglio^{47c}. Somogyi^{47d}. Gray and Somogyi^{47e}.

For the same reason, patients with acute and chronic localized and generalized infections, toxemias or drug effects were also excluded. The data from the group of "normal" hospital patients thus selected furnished valuable complement to the data obtained from the group of "healthy

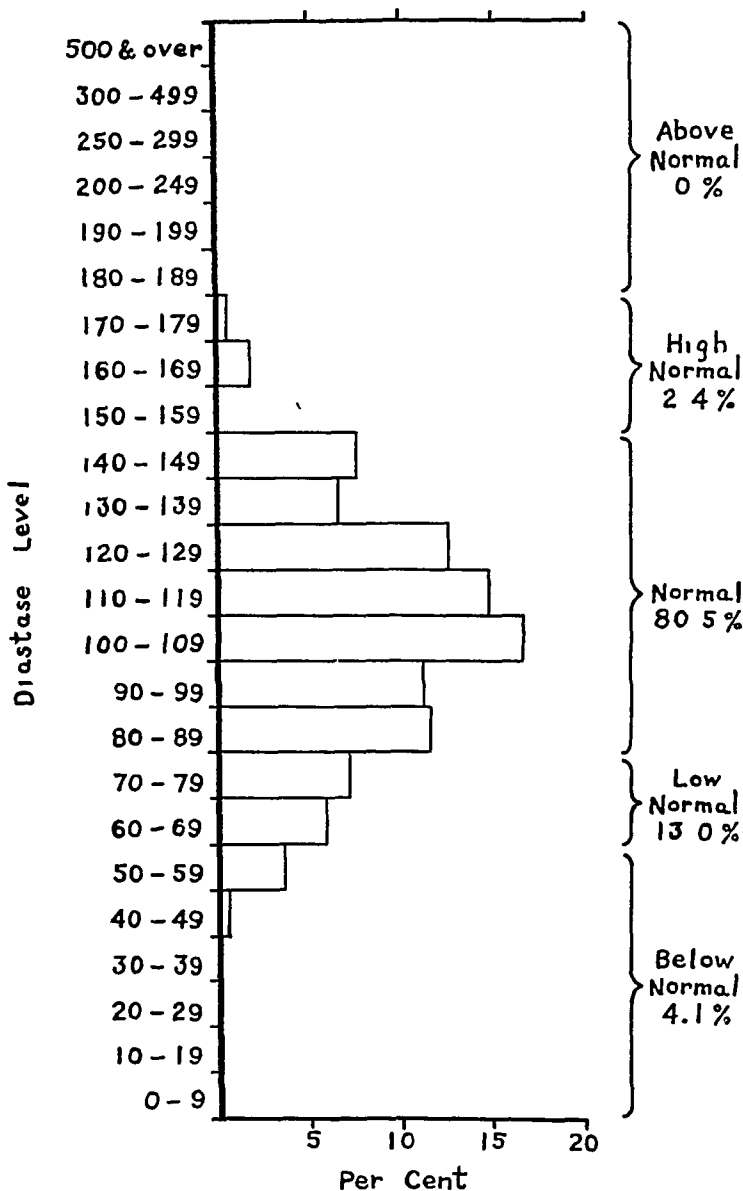


Fig 1—Range of distribution of blood diastase values of healthy persons

normal" persons. The levels for the former group, as may be seen in figure 2, show a wider spread over the scale than those for the latter.

Only 59.5 per cent of them come within the range of 80 to 150, another 17.7 per cent come between 60 and 80, and 6.5 per cent come between 150 and 180. There remain 12.6 per cent in the definitely sub-normal range, below 60 and 3.7 per cent in the high range, above 180.

The shift in the scale, as may be seen, shows in the main a tendency toward the lower range. Since subnormal diastase levels indicate some impairment of hepatic function,²⁵ it appears to me that a certain number of the "normal" hospital patients may have had some minor degree of

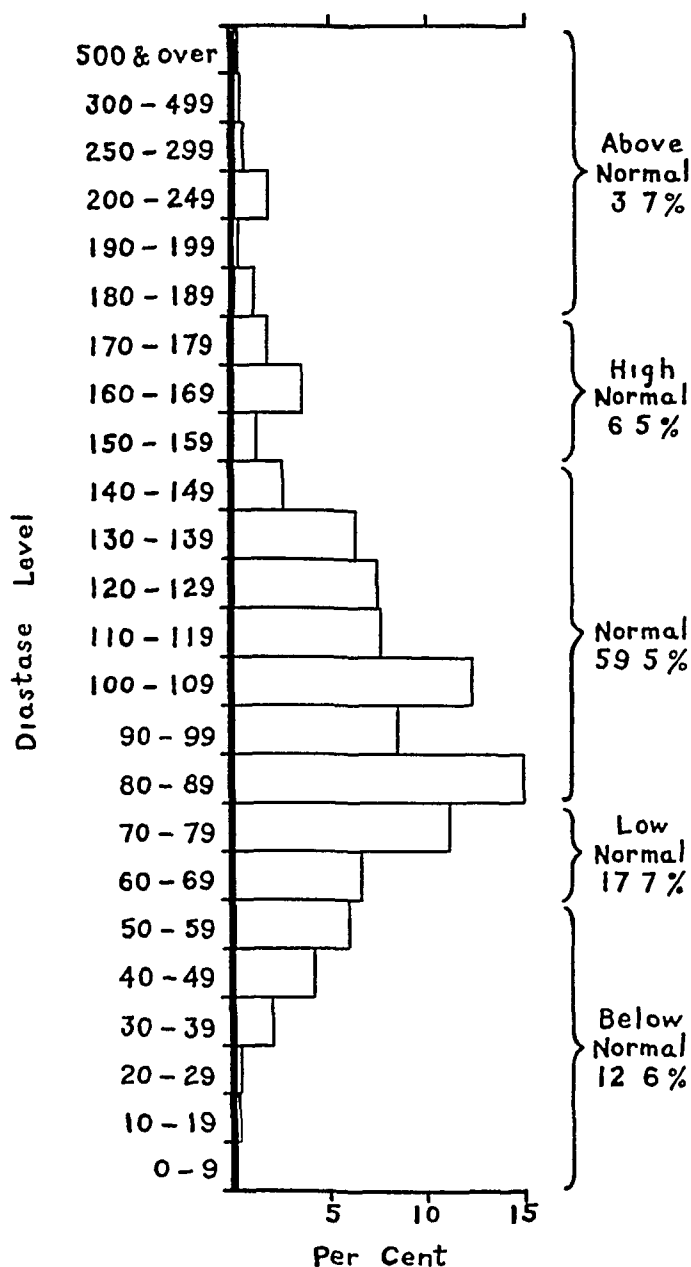


Fig 2—Range of distribution of blood diastase values of "normal" hospital patients

hepatic impairment, without apparent hepatic disease. This assumption may also apply to a lesser extent to a few of the "healthy normal" subjects. That the number of suspected cases should be higher among "normal" hospital patients than among healthy normal persons is a circumstance to be expected.

Effect of Age and Sex—Detailed analysis of both the normal groups disclosed the fact that age is virtually without influence on the diastase values in adults. In newborn infants, however, complete absence of diastase has been noted.⁴⁹ The enzyme usually first appears at the age of 2 months, it can be measured quantitatively at 3 months and reaches a relatively normal level in about a year.

Differences in diastase values due to sex were entirely negligible.

Effect of Food—Since the ingestion of food is followed by an increased secretion of both salivary and pancreatic diastase into the alimentary tract, the effect of food on the blood diastase was subjected to considerable study. Practically all investigators have agreed that neither the amount nor the type of food in any way alters the diastase level.⁵⁰ Prolonged periods of fasting⁵¹ and of dehydration¹⁷ likewise were found to be without effect. Diuresis, whether caused by excess intake of water⁵² or by section of the renal nerves,^{20d} exerts no influence on the diastase level in animals.

My own observations on human subjects have confirmed those of other workers as regards the lack of effect of food, fasting, diuresis, dehydration, exercise and sleep on the diastase content of blood.

ABNORMAL BLOOD DIASTASE LEVELS

While I consider normal values to be those between 80 and 150, changes in the level in the same person even within this range may be significant. For example, a diastase value of 90 is well within the normal range, but if a person has been known to have a usual blood diastase level of 140 and subsequently shows a level of 90, then the latter is subnormal in this particular instance. Too much significance should not be attached to a single value that falls in the borderline ranges, and the line between normal and abnormal should not be drawn too rigidly. One can only say that a single value on either side of the

49 Korowin. Ueber die fermentative Wirkung des pankreatischen Saftes und der Glandula parotis von Neugeborenen und Brustkindern auf Stärke, Jahresb u d Fortschr d Thier-Chem **3** 159, 1894.

50 (a) Corbett, D. The Quantitative Estimation of Amylolytic Ferments in the Urine as a Measure of Certain Pathological Conditions, Quart J Med **6** 351, 1913. (b) Cohen, I. The Concentration of Diastase in the Urine Throughout the Day, Biochem J **20** 253, 1926. (c) Cope, O., Hagstromer, A., and Blatt, H. Activity of Blood Serum Amylase in Hypophysectomized Dog, Am J Physiol **122** 428, 1938. (d) Carlson and Luckhardt.^{4b} (e) Crandall and Cherry.^{20g} (f) Milne and Peters.^{23a} (g) Karsner, Koeckert and Wohl.^{23b} (h) Lewis and Mason.²⁴ (i) Cohen.³² (j) Elman and McCaughan.^{33a} (k) Zoepffel.^{39a} (l) Harrison and Lawrence.^{39b} (m) Stocks.^{47b}

51 Milne and Peters.^{23a} Elman and McCaughan.^{33a} Cope, Hagstromer and Blatt.^{50c}

52 King.¹⁷ Reid and Narayana.^{23d}

normal range should prompt closer studies and observations on the patient. Repetition of determinations of diastase in suspected cases is always desirable as a means for the detection of abnormalities. The determination of diastase attains real clinical significance in the large number of instances in which the values are obviously abnormal, namely, when they fall below 60 or rise above 200.

CONCLUSIONS

Blood diastase is identical in nature with salivary and pancreatic diastase. This statement is based on the analysis by newer methods of the cleavage products of starch and glycogen produced by diastase derived from these several sources.

The origin of the diastase contained in normal blood is at present unknown. Conclusive experimental evidence shows that under normal physiologic conditions neither the pancreas nor the salivary glands contribute to the diastase content of the blood. My own observations indicate that the liver does not supply diastase to the blood.

Certain acute pathologic changes of the pancreas and salivary glands may result in a temporary effusion of diastase from these glands into the blood stream, causing an increased diastase content of the blood.

About 80 per cent of healthy ambulatory adults have blood diastase levels between 80 and 150, the remainder have levels falling either in the low range, between 60 and 80, or in the high range, between 150 and 180. Blood diastase values below 60 and above 200 are considered abnormal.

The diastase content of the blood of one person is maintained under normal conditions at a fairly constant level and is unaffected by the usual physiologic functions.

Progress in Internal Medicine

BRIGHT'S DISEASE

A REVIEW OF RECENT LITERATURE

WILLIAM S McCANN, M D

ROCHESTER, N Y

During the past year few basically new contributions have been made to the literature in this field, although there has been considerable elaboration in detail of lines of investigation previously established. Progress may be reported in the study of the formation of the pressor substance of the kidney and the conditions governing its action. Anti-pressor substances are described and their therapeutic possibilities considered. The possibilities and limitations of surgical intervention in various ways in the treatment of hypertension may be more accurately evaluated. Improvements in the management and chemotherapy of infections of the kidneys and the urinary passages offer hope of preventing many of the disastrous cardiovascular and renal sequelae of such infections, both in pregnant and in nonpregnant women. Considerable progress continues to be made in the investigation of normal renal function and the extension of this study into the field of pathologic physiology, thus laying the groundwork for future prophylaxis and therapy. Relatively little that is new marks the study of experimental nephritis or the clinical study of glomerulonephritis, aside from indications of the immunologic mechanisms involved in the former and the demonstration of qualitative as well as quantitative alterations in the plasma proteins in the nephrotic stages of the latter.

GLOMERULONEPHRITIS

In studying the experimental nephritis which is produced in rabbits by injection of nephrotoxic duck serum, Kay¹ finds that the nephritis is not caused by the union of anti-rabbit-kidney antibodies of nephrotoxic duck serum with the antigen of rabbit kidney. This union occurs quickly after the injection, yet a delay occurs in the appearance of the nephritis.

From the Department of Medicine, University of Rochester School of Medicine and Dentistry, and the Medical Clinic of the Strong Memorial and Rochester Municipal Hospitals.

1 Kay, C F. The Mechanism by Which Experimental Nephritis Is Produced in Rabbits Injected with Nephrotoxic Duck Serum, *J Exper Med* **72** 559 (Nov) 1940.

During this latent period, Kay finds, antibodies to duck serum proteins are being formed in the rabbit. As these are being formed they react with duck serum proteins in the rabbit and cause the latter to disappear. When the antibodies to duck proteins of the rabbit react with the anti-rabbit-kidney bodies bound in the kidney, nephritis results. Kay observed that if the rabbits are exposed to roentgen radiation no antibodies to duck serum are formed and no nephritis results. He cites some experiments of Saire, who clamped one renal vessel for fifteen minutes after injection of nephrotoxic duck serum and then released it. During this brief period the antikidney substance in the duck serum was bound in the other kidney only. After an interval unilateral nephritis resulted. Kay also found that the experimental nephritis develops more quickly after injection of the nephrotoxic duck serum in rabbits which have previously received injections of normal duck serum. This probably explains the shorter latent period of exacerbations of chronic glomerulonephritis as compared with the relatively long latent period of the initial attack, a phenomenon which has been described by many clinical observers.

Special attention has been given to exacerbations in a recent study by Seegal, Lyttle, Loeb, Jost and Davis². Of 68 patients with chronic glomerulonephritis under observation for periods of one to eight years, 13 experienced 28 exacerbations. These consisted of a sudden marked increase in hematuria with or without impairment of renal function. They occurred more frequently in young persons than in old. In all 13 patients the exacerbations were found to follow infection with hemolytic streptococci of group A. In 5 instances additional exacerbations occurred, which were not proved to follow infections with such organisms. The whole series of 68 patients experienced 350 infections during the course of observation. Only 68 of these infections were due to hemolytic streptococci. Many of the latter infections were not followed by exacerbations. The latent period before exacerbation was one to four days. The chief effect observed was a transient decrease in renal function.

Hayman and Martin³ have reviewed the data in 77 cases of acute nephritis, in 10 of which the patients died during the acute stage of the disease. Of the 67 patients who survived, 52 were followed for periods of six months to eight years. About two thirds of these recovered completely.

2 Seegal, D., Lyttle, J. D., Loeb, E. N., Jost, E. L., and Davis, G. On the Exacerbation in Chronic Glomerulonephritis, *J. Clin. Investigation* **19** 569 (July) 1940.

3 Hayman, J. M., Jr., and Martin, J. W., Jr. Acute Nephritis. A Review of Seventy-Seven Cases, *Am. J. M. Sc.* **200** 505 (Oct.) 1940.

The precipitating infection was demonstrated in 75 patients. In the majority of instances, about 75 per cent, the infection involved the upper respiratory tract, the throat, the sinuses and the ears. The acute onset occurred most frequently before the age of 30. Among older patients the onset tended to be more insidious, the symptoms less dramatic and the prognosis worse.

The role of infections of the skin in the production of glomerulonephritis is discussed by Futcher,⁴ who reviews the fairly extensive literature of so-called impetigo nephritis. Attention is called to the fact that there is evidence of a streptococcic as well as a staphylococcic infection in impetigo. In 11 of 153 cases of glomerulonephritis observed at the Johns Hopkins Hospital the disease followed a cutaneous infection. It is significant, however, that beta hemolytic streptococci were repeatedly found in cultures of material from the throat in 7 of the 11 cases. Healing of the nephritis occurred in all of Futcher's cases but 1. In this instance the cutaneous infection persisted for two months after the onset of the nephritis, which progressed after healing of the cutaneous infection.

The criteria for differential diagnosis of acute diffuse glomerulonephritis and "focal" nephritis are discussed by Payne and Illingworth.⁵ Many writers in the past have emphasized the presence or absence of edema, oliguria and hypertension as factors important in the differentiation of these conditions. Payne and Illingworth find these criteria useless in distinguishing the diseases at onset, in the light of subsequent developments. Their experience leads them to believe that "focal" nephritis as an entity is nonexistent.

Illingworth⁶ also discusses the relation of tonsillectomy to nephritis of childhood, marshaling evidence against tonsillectomy, which he believes may predispose to nephritis or may actually precipitate an attack. In his experience it does not either cure the disease or prevent its going on into the chronic stage.

Some relation of allergy to nephritis is suggested in a case reported by Daniels,⁷ that of a young woman with chronic urticaria and steatorrhea of one to two years' duration. After an injection of liver extract for anemia progressive nephritis, characterized by nephrotic edema, persistent hypertension and azotemia and eclamptic seizures, developed.

4 Futcher, P. H. Glomerular Nephritis Following Infections of the Skin, *Arch Int Med* **65** 1192 (June) 1940.

5 Payne, W. W., and Illingworth, R. S. Acute Nephritis in Childhood with Special Reference to Diagnosis of Focal Nephritis, *Quart J Med* **9** 37 (Jan) 1940.

6 Illingworth, R. S. Tonsillectomy and Nephritis of Childhood, *Lancet* **2** 1013 (Nov 11) 1939.

7 Daniels, A. P. Intolerance renale par hyperergie, *Acta med Scandinav* **104** 225, 1940.

After demonstration by cutaneous reaction of sensitivity to a number of animal proteins, a vegetarian diet was prescribed, with the result that the skin became normal and the renal condition improved. Death followed an intercurrent infection of the respiratory tract. Necropsy was not performed.

Cases of this type are seen occasionally by internists. While Daniels' assumption is tempting, it must not be too readily accepted, since many aspects of a complete investigation of this case have not been considered.

A consideration of the character of the renal lesions which are sometimes found in cases of disseminated lupus erythematosus is pertinent at this point. Stickney and Keith⁸ have studied the kidneys in 15 cases. In 8 no definite renal abnormality was noted. In 2 cases glomerulonephritis was found, but in each the renal lesions preceded the cutaneous disease. In the remaining cases the most definite lesions observed were some proliferation of the glomerular endothelium together with irregularity and thickening of the basement membrane. As a result of these studies, the authors find that a distinct renal lesion is not peculiar to lupus erythematosus.

NEPHROTIC STATES

Considerable attention is now being focused on the changes in the plasma proteins in nephrotic states. Melnick, Field and Parnall⁹ believe that the albumin and globulin fractions, as determined by the usual salting-out procedure, probably represent two independent protein systems, within each of which dissociation or association phenomena may occur in vitro (formation of smaller or larger complexes in the dispersed phase), with variable effects on the osmotic pressure. By means of this concept they interpret the observations made by Yanagi¹⁰ in my laboratory. He found that the osmotic pressure reached a maximum in six to seven hours, after which it decreased.

Luetscher¹¹ has studied the plasma and urinary proteins, using the Tiselius electrophoresis apparatus. He finds two components of normal albumin at a p_H of 4.0. In nephrotic states the ratio of these two components is altered both in the serum and in the urine, indicating that the albumin is changed in such states.

8 Stickney, J. M., and Keith, N. Renal Involvement in Disseminated Lupus Erythematosus, *Arch. Int. Med.* **66** 643 (Sept.) 1940.

9 Melnick, D., Field, H., Jr., and Parnall, C. G., Jr. Significance of the Albumin-Globulin Ratio of Serum, *Arch. Int. Med.* **66** 295 (Aug.) 1940.

10 Yanagi, K. A Clinical and Experimental Study of the Stability of the Colloid Osmotic Pressure of Serum Protein, *J. Clin. Investigation* **14** 853 (Nov.) 1935.

11 Luetscher, J. A., Jr. Electrophoretic Analysis of Plasma and Urinary Proteins, *J. Clin. Investigation* **19** 313 (March) 1940.

A similar conclusion is reached by Goettsch and Lyttle,¹² who employed precipitin reactions in the study of the plasma proteins in cases of nephrosis. In 23 cases studied they found alterations in both the albumin and the globulin fraction. The altered globulin fraction formed antibodies in the rabbit which would not react with normal serum globulin. In 1 case the albumin fraction was so altered that it was incapable of exciting antibody formation in the rabbit.

No relation could be discovered between these changes and the susceptibility to infection or the degree of proteinuria, cholesteremia or edema. In cases of acute nephritis the protein changes were minimal.

The nephrotic lesions found in cases of fatal pyloric and high intestinal obstruction have been discussed by Martz¹³ and by Pérez-Castro¹⁴. Deposits of calcium and degenerative changes in the tubular cells are frequently found. Martz explains the phenomenon by the fact that, in spite of the alkalosis of the blood in these conditions, the kidney may continue to secrete an acid urine in an attempt to conserve fixed base, which is steadily diminishing in body fluids. Under these circumstances the alkalinity of the parenchymal cells may become sufficient to permit precipitation of calcium within them.

A timely warning against the indiscriminate use of hypertonic solutions of sucrose is issued by Anderson and Bethea¹⁵. They noted a peculiar foamy swelling of the cells of the convoluted tubules in the course of routine autopsies. Investigation revealed that in these cases intravenous injections totaling 100 to 3,350 cc of a 25 per cent solution of sucrose had been given. By the use of such concentrations renal lesions may be produced in animals. The authors consider that the administration of hypertonic solutions of sucrose is inadvisable in patients with renal damage and that large or repeated doses should be avoided.

In the treatment of nephrotic edema Goudsmit and Binger¹⁶ still recommend the use of solutions of acacia, as they have noted none of the disastrous results previously recorded by others. They claim success in 90 per cent of cases in which treatment consisted of rest in bed, a salt-free high protein diet, restriction of fluids, oral administration of

12 Goettsch, E, and Lyttle, J. D. Precipitin Studies of Nephrosis and Nephritis, *J Clin Investigation* **19** 9 (Jan) 1940

13 Martz, H. Renal Calcification Accompanying Pyloric and High Intestinal Obstruction, *Arch Int Med* **65** 375 (Feb) 1940

14 Pérez-Castro, E. Nefrosis calcicas en las estenosis pilorica y duodenal, *Semana med españ* **3** 1015 (Aug 17) 1940, abstracted, *J A M A* **115** 1410 (Oct 19) 1940

15 Anderson, W. A. D., and Bethea, W. R. Renal Lesions Following Administration of Hypertonic Solutions of Sucrose. Report of Six Cases, *J A M A* **114** 1983 (May 18) 1940

16 Goudsmit, A., Ji, and Binger, M. W. The Treatment of Nephrotic Edema, *J A M A* **114** 2515 (June 29) 1940

potassium nitrate (9 mg daily) and intravenous injection of a 6 per cent solution of acacia in a 0.06 per cent solution of sodium chloride (500 cc on successive or alternate days for not more than three or four doses) No untoward reactions were noted other than urticaria, for which epinephrine hydrochloride was given, and pain in the chest

In view of the increasing availability of serum or plasma dried by the lyophile process for use in concentrations several times that of normal plasma, it is probable that the introduction of a foreign colloid like acacia will no longer be necessary Aldrich and Boyle¹⁷ have employed such concentrated solutions of serum protein as a diuretic in patients with nephrosis, with excellent results Diuresis ensued and in most instances continued until the edema was completely eliminated and in some instances the nephrosis cured This treatment was not effective if hematuria or acute infection was present The earlier patients were treated in this manner, the better was the result, so that it is regarded as the method of first choice and not as a last resort Pooled human serum was used in a concentration four times normal An initial dose of 25 to 65 cc was given If diuresis did not ensue in two or three days, further doses were given, to the maximum of four In most instances only one or two injections were required

RENAL HYPERTENSION

Experimental Studies—There is great investigative activity in the field of renal hypertension The results obtained have led to somewhat divergent and conflicting conclusions among the various investigators, though agreement has been reached on certain points Page¹⁸ has recently reviewed much of the literature on experimental hypertension, including the hypertension induced by injection of kaolin into the cerebrospinal space and by denervation of the carotid sinus, as well as the work on hypertension induced by the Goldblatt technic This article will be helpful in the orientation of the confused reader

Page and Helmer have observed that renin is combined with a renin activator to form a substance which they call angiotonin From the Physiological Institute in Buenos Aires there has been reported work of similar import Muñoz, Braun-Menendez, Fasciolo and Leloir¹⁹ review their work on "hypertensin" This substance is produced by

17 Aldrich, C A, and Boyle, H H Concentrated Human Blood Serum as a Diuretic in Nephrosis, *J A M A* **114** 1062 (March 23) 1940

18 Page, I H Newer Aspects of Experimental Hypertension in Blood, Heart and Circulation Symposium, Publication 13, American Association for the Advancement of Science, Washington, D C, 1940

19 Muñoz, J M, Braun-Menendez, E, Fasciolo, J C, and Leloir, L F The Mechanism of Renal Hypertension, *Am J M Sc* **200** 608 (Nov) 1940

the action of renin (an enzyme) on blood globulin as substrate (hypertensin precursor) Hypertensin is found to have a direct vasoconstrictor action Its chemical and pharmacologic properties have been studied An enzyme has been found which destroys hypertensin This is called hypertensinase Methods have been described for the estimation of these substances After the injection of renin into an animal the hypertensin precursor decreases or disappears from the blood After nephrectomy the hypertensin precursor increases and hypertensinase decreases Hypertensin is regarded as identical with the angiotonin of Page and Helmer No tachyphylaxis occurred after repeated injections of hypertensin, such as was previously described by Page and Corcoran for renin

Page and Helmer ²⁰ find that angiotonin causes strong contractions of isolated segments of intestine Page has utilized this as a method of ascertaining the renin-activating power of plasma By this means he demonstrated angiotonin in the blood of both human and canine subjects with renal hypertension From these observations he suggests that the blood of subjects with such disease possesses either an increased amount of renin activator or a diminished amount of angiotonin inhibitor or both

Page ²¹ reports observations demonstrating the liberation of renin into the blood stream from kidneys of animals rendered hypertensive by means of perinephritis induced with cellophane It is found in the blood of the renal vein of such animals, but disappears by the time it reaches the femoral artery The amount of activator is increased by the time it reaches the femoral artery Early in the course of severe hypertension large amounts of renin are liberated Later the amounts of both activator and angiotonin may be reduced by the development of inhibitors, which were found by Page and his associates ²² to be produced both in kidney and in muscle

From the foregoing account a close parallelism is seen between the observations of workers in this country and those in Argentina The main facts established are that renin activates, or is activated by a substance in normal blood, with the formation of a pressor substance, against which inhibiting substances may be developed The South American workers believe both renin and the inhibiting substances to be enzymes

20 Page, I H, and Helmer, O M A Crystalline Pressor Substance (Angiotonin) Resulting from the Reaction Between Renin and Renin-Activator, *J Exper Med* **71** 29 (Jan) 1940

21 Page, I H Difference in the Activating Effect of Normal and Hypertensive Plasma on Intestinal Segments Treated with Renin, *Am J Physiol* **130** 29 (July) 1940

22 Page, I H, Helmer, O M, Kohlstaedt, K G, Fouts, P J, Kempf, G F, and Corcoran, A C Substance in Muscle Eliciting Prolonged Reduction of Blood Pressure in Human and Experimental Hypertension, *Proc Soc Exper Biol & Med* **43** 722 (April) 1940

Prinzmetal, Lewis and Leo²³ claim to be the first to demonstrate a pressor substance derived from the ischemic kidney. They point out that renin had been prepared from the renal cortex, but that renin itself was not the actual pressor substance. When the circulation to the kidney is completely interrupted, a pressor substance accumulates ("ischemin"). This substance is easily washed out when renal circulation is reestablished or when artificial perfusion is performed. Further studies are reported²⁴ in which the authors found that the normal kidney secretes little or no renin. Perfusates of blood-free ischemic kidneys were found to contain more renin than those of kidneys that were blood filled. Renin is not thermostable, yet on incubation with plasma it yields a heat-stable pressor substance.

The behavior of the renal blood flow after partial constriction of the renal artery has been studied by Schroeder and Steele,²⁵ who employed thermistomuhurs to record the blood flow and Hamilton optical manometers to record the blood pressure. The clamp used to constrict the renal artery was arranged so as to be adjustable externally. The artery was progressively constricted. After each new constriction, a tendency was noted for the blood flow to return to the normal level, until a marked degree of constriction had been produced. This phenomenon is believed to be due to compensatory dilatation of the renal arterial tree beyond the constriction. These dilated vessels were found to be in a state of extraordinary sensitivity to epinephrine, since the administration of minute doses of this drug (0.05 microgram of epinephrine hydrochloride per kilogram of body weight) was found to cause complete cessation of renal blood flow for considerable periods. Arterial hypertension of a significant degree sometimes followed partial constriction of one renal artery during brief experiments in which epinephrine was given. These experiments contribute further evidence in support of the view that the control of the renal circulation is largely independent of the systemic circulation. Mason, Robinson and Blalock²⁶ found that in experiments based on the Goldblatt technic there is no constant relation between the systemic arterial pressure and the pressure in the renal artery distal to the point of constriction. The hypertension induced may persist even though the renal arterial pressure returns to normal.

23 Prinzmetal, M., Lewis, H., and Leo, S. D. Etiology of Hypertension Due to Complete Renal Ischemia, *Proc Soc Exper Biol & Med* **43** 696 (April) 1940.

24 Prinzmetal, M., Lewis, H. A., and Leo, S. D. The Etiology of Hypertension Due to Complete Renal Ischemia, *J Exper Med* **72** 763 (Dec.) 1940.

25 Schroeder, H. A., and Steele, J. M. The Behaviour of Renal Blood Flow After Partial Constriction of the Renal Artery, *J Exper Med* **72** 707 (Dec.) 1940.

26 Mason, M. F., Robinson, C. S., and Blalock, A. Studies of the Renal Arterial Blood Pressure and the Metabolism of Kidney Tissue in Experimental Hypertension, *J Exper Med* **72** 289 (Sept.) 1940.

Kohlstaedt and Page²⁷ studied the mechanics of the renal circulation in regard to the liberation of renin in perfused kidneys. An elaborate scheme for pulsating artificial perfusion of isolated kidneys with defibrinated blood was devised. Under these conditions renal blood flow, urinary secretion and oxygen consumption of the kidney were maintained, but values for urea clearance were low. Reduction of the pulse pressure of the perfusion was accomplished by constriction of the renal artery without altering the mean pressure. When the kidneys were perfused at normal pulse pressures no increase in renin in the perfused venous blood was found after three hours. When the pulse pressure was reduced the venous blood was found at the end of one hour to have a markedly increased power of constricting the blood vessels of a rabbit's ear. Perfusion of a dog's hindleg under similar conditions did not cause such a change in the venous blood.

Further experiments by Corcoran and Page²⁸ confirm the previous observations of these investigators to the effect that renin causes a reduction in renal blood flow and an increase in the filtration fraction, attributed to constriction of the efferent glomerular arterioles. Steele and Schroeder,²⁹ on the contrary, found that the injection of renin was usually followed by an increase in renal blood flow. They employed aqueous extracts of kidney from which depressor substances had been removed. Their observations suggest that the absence of depressor substances accounts for the divergence of results from those previously reported by Merrill, Williams and Harrison, though in my opinion this would not explain the divergence from the findings of Corcoran and Page.

Landis, Jeffers and Shiels³⁰ discuss the biologic assay of homologous heated renal extracts. With homologous extracts tachyphylaxis can be avoided if the tests are repeated at intervals of more than twenty-four hours. With heterologous extracts anaphylactic phenomena may accompany the second injection. As to the activity of extracts, that from rabbit was most active, that from guinea pig next active and those from man and dog least active. As to the reactivity of species, the rat and

27 Kohlstaedt, K. G., and Page, I. H. The Liberation of Renin by Perfusion of Kidneys Following Reduction of Pulse Pressure, *J. Exper. Med.* **72** 201 (Aug.) 1940.

28 Corcoran, A. C., and Page, I. H. The Effects of Renin on Renal Blood Flow and Glomerular Filtration, *Am. J. Physiol.* **129** 698 (June) 1940.

29 Steele, J. M., and Schroeder, H. A. Effect of Renal Extract (Renin) upon the Flow of Blood Through Various Organs, *J. Clin. Investigation* **18** 477 (July) 1939.

30 Landis, E. M., Jeffers, W. L., and Shiels, E. H. The Pressor Effects of Homologous and Heterologous Injections of Heated Kidney Extracts, *Am. J. Physiol.* **128** 672 (March) 1940.

guinea pig were more reactive than dog and rabbit when equivalent doses were injected

Beckwith and Chanutin³¹ found that saline extracts of the remnants of kidney after partial nephrectomy produced little or no pressor effects when tested on normal rats. This is in marked contrast to the consistent and striking pressor effects which were obtained with extracts of normal rat kidney.

The presence of a vasoconstrictor substance in the blood of men and dogs with hypertension has been demonstrated by Page,³² who found that it was not present in the blood of normal men and dogs. Small amounts of plasma to be tested were added to blood of dogs which had both kidneys removed, and this mixture was perfused through a rabbit's ear. The action of the pressor substance, angiotonin, is said to be greatly enhanced by this procedure, since the blood of nephrectomized dogs lacks inhibiting substances present in that of normal animals.

Freeman³³ reports that the blood of normal dogs contains anti-pressor substances, which are not found in the blood of dogs with hypertension. The antipressor substances exert no effect on dogs with normal blood pressure.

Dock³⁴ reports that when rabbits with renal hypertension are pithed the blood pressure falls as low as that in normal controls. He gives evidence in support of the view that the humoral agent responsible for renal hypertension sensitizes both the vasomotor center and the arterial response of epinephrine. Ogden, Brown and Page³⁵ found that before the onset of hypertension and in the early stages of this condition animals gave abnormally great pressor responses to noise or fright and to injections of pitressin as compared with normal animals which had been subjected to the same operative procedure without constriction of the renal arteries. This heightened reactivity is believed to reside in the muscular coat of the arteries.

Wakerlin and Gaines³⁶ studied the effects of various agents on dogs with renal hypertension. Estrone, testosterone propionate, liver extract,

31 Beckwith, J. R., and Chanutin, A. The Pressor Effect of Kidney Extracts of Intact and Partially Nephrectomized Rats, *Am J Physiol* **128** 562 (Feb.) 1940

32 Page, I. H. The Vasoconstrictor Action of Plasma from Hypertensive Patients and Dogs, *J Exper Med* **72** 301 (Sept.) 1940

33 Freeman, G. Antipressor Effect of Normal Blood in Experimental Hypertension, *Proc Soc Exper Biol & Med* **45** 185 (Oct.) 1940

34 Dock, W. Vasoconstriction in Renal Hypertension Abolished by Pithing, *Am J Physiol* **130** 1 (July) 1940

35 Ogden, E., Brown, L. T., and Page, E. W. The Increased Sensitivity of Arterial Muscle in the Pre-Hypertensive Phase of Experimental Renal Hypertension, *Am J Physiol* **129** 560 (June) 1940

36 Wakerlin, G. E., and Gaines, W. The Effects of Various Agents on the Blood Pressure of Renal Hypertensive Dogs, *Am J Physiol* **130** 568 (Sept.) 1940

pancreatic extract, garlic and parsley, fresh hog kidney, adrenal cortical extract, extract of whole pituitary and solution of posterior pituitary were without effect

Katz and Steinitz³⁷ report that the pulmonary arterial pressure is not elevated in cases of the systemic hypertension induced by renal ischemia

The condition of the retinal arteries in experimental hypertension has been carefully studied by Laughlin, Thomas and Friedenwald³⁸ The hypertension was induced by the Goldblatt technique Retinal changes were recorded by drawings and photographs, after which the eye was enucleated and the retina sectioned for the purpose of correlating the ophthalmoscopic appearance with histologic changes In vessels showing localized constrictions no correlation was found between the constrictions and the microscopic appearance of the vessel wall The constrictions are believed to be due to spasm Abnormalities of the wall of the vessels occurred in segments not constricted The histologic changes closely resembled those found in cases of essential hypertension in man, in the vessels of the viscera and muscles as well as in those of the retina

COLLATERAL CIRCULATION

Incidental note is made of the evidence that collateral circulation is established in kidneys with a high degree of constriction of the renal arteries or in those with thrombotic occlusion The collateral vessels entered from the capsule and also from an artery running beside the ureter, forming an anastomosis with the renal artery at the hilus of the kidney³⁸ Page¹⁸ also mentions development of collateral circulation Stewart,³⁹ reporting a case of severe hypertension with marked narrowing of the orifices of the renal arteries, notes the importance of aberrant vessels In this case the kidneys had some of the appearance of those in cases of pyelonephritis He believes the arterial narrowing was responsible for the major change, since a part of a kidney supplied by an aberrant vessel was relatively well preserved Experimentally efforts have been made by MacNider and Donnelly⁴⁰ to establish an adventitious

37 Katz, L N, and Steinitz, F S Pulmonary Arterial Pressure in Experimental Renal Hypertension, *Am J Physiol* **128** 433 (Feb) 1940

38 Laughlin, R C, Thomas, C B, and Friedenwald, J S The Retinal Arteries in Experimental Renal Hypertension The Significance of Localized Caliber Constriction, *Bull Johns Hopkins Hosp* **67** 79 (Aug) 1940

39 Stewart, C F Arteriosclerosis of the Renal Artery Orifices with Severe Hypertension, *J A M A* **114** 2099 (May 28) 1940

40 MacNider, W de B, and Donnelly, G L Value of Omentopexy in Establishing an Adventitious Circulation in the Normal Kidney, *Proc Soc Exper Biol & Med* **40** 271 (Feb) 1939

circulation in the kidney. Similarly, Weeks, Steiner, Mansfield and Victor⁴¹ were able to reduce the blood pressure of dogs with experimental renal hypertension by means of splenorenopexy, which provides collateral circulation between the splenic sinusoids and the capillaries about the renal tubules. The glomeruli were not usually involved in this collateral circulation. After removal of the fused spleen and kidney the blood pressure returned to the previous level of hypertension.

A personal communication from Ask-Upmark, of Lund, Sweden, reports that his colleague, Bergendal, subsequently found hypertension in some patients in whom aberrant vessels had been ligated for relief of hydronephrosis. In one of my cases discussed later,⁴² the ligation of an aberrant vessel interfered with the relief of hypertension by nephropexy in a patient with orthostatic hypertension who had previously shown a marked fall in pressure during recumbency. Thus from a variety of sources comes evidence of the importance of the contribution of aberrant vessels to the renal circulation. These vessels should not be ligated without good reason lest the resulting partial ischemia contribute to hypertension.

CLINICAL HYPERTENSION

In previous reviews the urologic aspects of "essential" hypertension were shown to have received a great deal of attention. The interest in this field continues to be actively manifested, though warnings have been issued against too great expectations engendered by unbalanced enthusiasm for surgical relief of hypertension associated with urologic conditions.

Success following nephrectomy continues to be reported in cases of certain unilateral renal conditions. Koons and Ruch⁴³ describe the case of a child of 7 with a Wilms tumor in which nephrectomy relieved the hypertension. Since the tumor mass surrounded the kidney, it was suggested that it may have caused renal ischemia in much the same way as did the cellophane perinephritis induced by Page for the production of experimental hypertension. The tumor itself was not the source of pressor substances, since there were extensive metastases, which would have perpetuated the hypertension after nephrectomy if the tumor had

41 Weeks, D. M., Steiner, A., Mansfield, J. S., and Victor, J. The Depressor Effect of Spleno-Reno-Pexy on Hypertension Due to Renal Ischemia, *J. Exper. Med.* **72** 345 (Oct.) 1940.

42 McCann, W. S., and Romansky, M. J. Orthostatic Hypertension. The Effect of Nephroptosis on the Renal Blood Flow, *J. A. M. A.* **115** 573 (Aug. 24) 1940.

43 Koons, K. M., and Ruch, M. K. Hypertension in a Seven Year Old Girl with Wilms' Tumor Relieved by Nephrectomy, *J. A. M. A.* **115** 1097 (Sept. 28) 1940.

been the source Patch, Rhea and Codnere⁴⁴ report successful relief of hypertension in a girl of 12 following unilateral nephrectomy for chronic atrophic pyelonephritis involving the right kidney only The left kidney was hypertrophied, but otherwise was entirely normal Barker and Walters⁴⁵ also report 5 cases in which relief was obtained after nephrectomy for unilateral atrophic pyelonephritis In reviewing a series of cases encountered at the Mayo Clinic, the authors found that there was serious hypertension in slightly less than half of those cases in which pathologic diagnosis of chronic atrophic pyelonephritis had been made after nephrectomy

The possibility of hypertensive sequelae to trauma of one kidney is considered by Nesbit and Ratliff⁴⁶ They suggest that such patients with renal trauma be followed carefully for some time, with a view toward nephrectomy should hypertension develop

Three more cases of malignant hypertension associated with unilateral narrowing of the orifice of the renal artery have been described by Saphir and Ballinger⁴⁷ In 2 of these arteriolosclerosis had developed in the other kidney In 1 instance renal insufficiency was induced by heart failure and in another by pyelonephritis in the contralateral kidney In the third case renal insufficiency did not occur, and in this case the arteriolonecrosis of malignant hypertension was not observed

Palmer, Chute, Crone and Castleman,⁴⁸ while recognizing the beneficial effects which frequently follow unilateral nephrectomy, point out that the urologic abnormality may be only incidental in the course of hypertension due to other causes They feel that, in general, nephrectomy should rarely be advised if the patient is a woman over 45 or a man over 50 They point out that congenital predisposition to hypertension is a factor which should not be overlooked and that they have observed many patients who have had pyelonephritis and obstruction for years without the development of hypertension The difference between those in whom it does develop and those in whom it does not is in the presence or absence of a congenital predisposition From the

44 Patch, F S , Rhea, I J , and Codnere, J T Hypertension in a Girl of Twelve Associated with Unilateral Chronic Atrophic Pyelonephritis, Treated by Nephrectomy, *Canad M A J* **43** 419 (Nov) 1940

45 Barker, N W , and Walters, W Hypertension and Chronic Atrophic Pyelonephritis, *J A M A* **115** 912 (Sept 14) 1940

46 Nesbit, R M , and Ratliff, R K Hypertension Associated with Unilateral Nephrectomy, *J Urol* **43** 427 (March) 1940

47 Saphir, O , and Ballinger, J Hypertension (Goldblatt) and Unilateral Malignant Nephrosclerosis, *Arch Int Med* **66** 541 (Sept) 1940

48 Palmer, R S , Chute, R , Crone, N L , and Castleman, B Renal Factor in Continued Arterial Hypertension Not Due to Glomerulonephritis, as Revealed by Intravenous Pyelography, *New England J Med* **223** 165 (Aug 1) 1940, abstracted, *J A M A* **115** 1054 (Sept 21) 1940

author's point of view the decision to perform a nephrectomy must be based on the following assumption that the lesion is not merely incidental, that there is no secondary vascular disease in the remaining kidney and that there is no recurring pyelitis of the other kidney

Schroeder and Fish⁴⁹ have continued studies on patients with so-called essential hypertension who have been found on urologic study to have organic renal lesions. Of 7 patients who had had unilateral nephrectomy, only 2 were definitely improved. They point out that unless suitable cases are selected many kidneys may be removed needlessly without benefit. In general, patients with long-standing hypertension of the malignant type are not suitable for this procedure. They do not favor operation in cases in which the hypertension is of more than two years' standing. The renal lesion should be strictly confined to one kidney and may reduce its function, but the total renal function must not be reduced if good results are to be expected. Also they feel that retinal changes should be absent and arteriolar changes should not be of severe character.

Crabtree and Chaset⁵⁰ and Braasch, Walters and Hammer⁵¹ sound notes of warning against undue expectations for relief of hypertension by surgical treatment of urologic lesions. Crabtree and Chaset find that hypertension in cases of pyelonephritis is not the rule. In 152 instances in which nephrectomy was done hypertension was not a common finding, although vascular disease was present in the kidneys removed in a high percentage of cases. Braasch, Walters and Hammer found the incidence of hypertension among 1,684 patients with surgical conditions of the kidney to be no higher than that in a similar group of people taken at random. Unilateral atrophic pyelonephritis is the lesion most likely to be amenable to surgical relief, although only 20 of 43 patients with such a lesion were found to have hypertension. Among patients with urolithiasis, hypertension was present in only 20 per cent of those who showed infection of the urinary tract and in only 5.7 per cent of those in whom no infection was present. Cortical abscess and perinephritic inflammations were found not to be factors in the production of hypertension. Obstruction of the urinary tract was also found not to be a factor unless it was bilateral.

"Orthostatic hypertension" is a term employed by McCann and Romansky⁴² to describe the condition of patients in whom marked

49 Schroeder, H. A., and Fish, G. W. Studies on "Essential" Hypertension. Effect of Nephrectomy upon Hypertension Associated with Organic Renal Disease, *Am J M Sc* **199** 601 (May) 1940.

50 Crabtree, E. G., and Chaset, N. Vascular Nephritis and Hypertension, *J A M A* **115** 1842 (Nov 30) 1940.

51 Braasch, W. F., Walters, W., and Hammer, H. J. Hypertension and the Surgical Kidney, *J A M A* **115** 1837 (Nov 30) 1940.

fluctuations in blood pressure may be brought about by change from the erect to the strictly recumbent posture. In making tests to discover such patients, preliminary records of the blood pressures are made while the person is ambulatory, after which he is put to bed and kept in strict recumbency for twenty-four to forty-eight hours, he is not permitted to sit up in bed to eat or to attend to excretory functions. If this procedure is followed by a well marked reduction in blood pressure, below the minimal levels previously observed, pyelograms are made with the patient in both the erect and the recumbent posture, and the observations on blood pressure are continued under ambulatory conditions. The authors studied several cases in which orthostatic hypertension was associated with nephroptosis, observing the diodrast and inulin clearances with the patient in the recumbent and in the erect posture. In these cases the diodrast clearance when the patient was in the erect posture was lower than when he was recumbent, from which it was concluded that the renal blood flow was less in the erect position. The inulin clearance, taken as a measure of the rate of glomerular filtration, was relatively constant, though the "filtration fraction" was increased when the patient was in the erect posture. From these observations it was inferred that nephroptosis, in some cases, resulted in partial renal ischemia when the patient was in the erect posture and then in orthostatic hypertension. It was recognized, however, that in many cases nephroptosis is unaccompanied by hypertension. Attempts at correction of the ptosis both by means of belts and by nephropexy were somewhat disappointing as far as complete relief of hypertension was concerned. These procedures did accomplish a great deal in the way of preventing wide variations in blood pressure of the patients, and this stabilization appeared to be an important factor in the relief of both cardiac and cerebral symptoms which frequently accompanied the critical elevations in pressure to which these patients are subject.

The questions concerning the value of certain neurosurgical operations for the relief of hypertension have received considerable discussion. Peet, Woods and Braden,⁵² who champion the resort to bilateral supra-diaphragmatic splanchnicectomy with lower dorsal sympathetic ganglionectomy, give the results of such treatment in 350 cases. They find that in slightly over half there were significant reductions in blood pressure, disability was improved in 81 per cent of cases, the condition of the eyegrounds in 70 per cent, the electrocardiogram in 53 per cent, renal function in 52 per cent and the concentration of the urine in 45 per cent. Such favorable results were not obtained by Davis and Barker.⁵³

⁵² Peet, M. M., Woods, W. W., and Braden, S. The Surgical Treatment of Hypertension, *J. A. M. A.* **115** 1875 (Nov. 30) 1940.

⁵³ Davis, L., and Barker, M. H. Clinical and Experimental Experiences in Surgical Treatment of Hypertension, *Am. J. Surg.* **110** 1016 (Dec.) 1939.

They found that bilateral splanchnic section alone failed to give relief to patients who had not previously obtained relief from therapy with thiocyanates unless the doses of these substances were pushed to toxic levels. However they did find that in some instances after splanchnic section the sensitiveness to the action of thiocyanates was increased. The authors believe that a majority of patients with hypertension respond favorably to the use of potassium thiocyanate with an appreciable decrease in both systolic and diastolic blood pressure.

Hopes of promising new developments in the treatment of hypertension have been raised by recent reports that antipressor substances may be extracted from kidney tissue. Harrison, Grollman and Williams⁵⁴ prepared extracts which when given orally or parenterally exerted no effect on normal rats except to diminish their response to renin, ephedrine and pitressin. When this substance was given orally or parenterally to rats with hypertension the blood pressure declined. Williams, Grollman and Harrison⁵⁵ found similar effects when it was given to dogs but noted certain toxic effects which may have been due to toxins or to nonspecific pressor substances characteristic of all tissue extracts. In a later report Grollman, Williams and Harrison⁵⁶ described its effects on patients with hypertension in whom it caused a decline in pressure in most instances. They describe its unique properties which distinguish it from depressor substances described by previous investigators.

The chemical properties and the type of action are entirely different from those of histamine, choline and the adenosine group of compounds. There likewise appear to be distinct differences from the products obtained by others from kidney, and although our extract has certain properties resembling those of urohypotensin and depressan it differs from these in that oral doses which cause marked decline in the blood pressure of animals with renal hypertension have little or no effect on the blood pressure of normal animals. So far as we know, no other substance has been described which has the properties of long duration of action, effectiveness by mouth and lack of reduction of blood pressure of normal animals as compared to marked reduction of blood pressure in animals with renal hypertension.

PREGNANCY AND RENAL DISEASE

Toxemias—The renal blood flow of women with toxemias of pregnancy has been measured by means of the diodrast clearance by Chesley

⁵⁴ Harrison, T. R., Grollman, A., and Williams, J. R., Jr. The Anti-Pressor Action of Renal Extracts and Their Capacity to Reduce the Blood Pressure of Hypertensive Rats, *Am J Physiol* **128**:716 (March) 1940.

⁵⁵ Williams, J. R., Jr., Grollman, A., and Harrison, T. R. The Reduction of the Blood Pressure of Hypertensive Dogs by the Administration of Renal Extract, *Am J Physiol* **130**:496 (Sept.) 1940.

⁵⁶ Grollman, A.; Williams, J. R., Jr., and Harrison, T. R. Reduction of Elevated Blood Pressure by Administration of Renal Extracts *J. A. M. A.* **115** 1169 (Oct. 5) 1940.

Connell, Chesley, Katz and Glissen⁵⁷ In patients with eclampsia (post-partum determinations), preeclampsia and recurrent toxemias the diodrast clearance was approximately in the same range as that found in normal women⁵⁸ These normal values are somewhat lower than those which have previously been reported from the laboratory of Homer Smith In pregnant women with chronic nephritis Chesley found the diodrast clearance considerably reduced

Pyelonephritis of Pregnancy—In a study of 45 cases Crabtree and Reid⁵⁹ found that the majority of women who had suffered from pyelonephritis of pregnancy had appreciable damage to their kidneys, though the function was usually adequate Only 6 of 45 had blood pressures above 150 systolic and 90 diastolic The authors are inclined to believe that pyelonephritis is generally a progressive disease, in a considerable number of cases the damage remains stationary at the level of original injury The prognosis is most grave for those women who have both pyelonephritis and toxemia The data did not indicate the extent to which life was shortened The authors feel that the aim of treatment should be to minimize the initial injury as soon as possible and to control the infection

Crabtree and Reid believe that there is now too great a tendency to terminate the pregnancy when pyelonephritis occurs, and they state that this policy is just as irrational as one which preserves the pregnancy at any cost to the mother short of death Traut, Bayer and McLane⁶⁰ and Mussey and Lovelady⁶¹ both outline methods of detecting the earliest prodromes of infection of the urinary tract and of managing the early stages in such a way that the more severe complications can be avoided Rest in bed, sedation and forcing of fluids are measures which alone ameliorate or relieve the condition in many cases The more recent use of chemotherapeutic agents has proved successful in controlling infection

57 Chesley, L C , Connell, E J , Chesley, E R , Katz, J D , and Glissen, C S The Diodrast Clearance and Renal Blood Flow in Toxemias of Pregnancy, *J Clin Investigation* **19** 219 (Jan) 1940

58 Chesley, L C , and Chesley, E R The Diodrast Clearance and Renal Blood Flow in Normal Pregnant and Non-Pregnant Women, *Am J Physiol* **127** 731 (Nov) 1939

59 Crabtree, E G , and Reid, D E Pregnancy Pyelonephritis in Relation to Renal Damage and Hypertension Clinical Study of Forty-Five Cases of Pyelonephritis More than Five to Ten Years After Infection, *Am J Obst & Gynec* **40** 17 (July) 1940, abstracted, *J A M A* **115** 963 (Sept 14) 1940

60 Traut, H F , Bayer, D S , and McLane, C M The Prophylaxis of Pyelo-Ureteritis Gravidarum, *J A M A* **115** 94 (July 13) 1940

61 Mussey, R D , and Lovelady, S B Pyelitis of Pregnancy and Its Management in One Hundred and Twenty-One Cases, *West J Surg* **48** 591 (Oct) 1940, abstracted, *J A M A* **115** 2315 (Dec 28) 1940

Cortical Necrosis—Madding, Binger and Hunt⁶² report a case of postpartum urinary suppression of long duration in which recovery ensued. It resembled those in which at autopsy cortical necrosis is found. In this instance the patient had taken quinine, and it is suggested that this drug may have caused the suppression, since the patient recalled that the taking of quinine on a previous occasion had caused a similar severe lumbar pain.

Penner and Bernheim⁶³ on reviewing the literature found that in the majority of instances bilateral cortical necrosis was preceded by a long period of shock, and this occurred in 2 cases which they report. Experiments led them to believe that marked vasospasm occurs in shock and that such spasm leads to cortical necrosis. In terms of histologic changes, the tubules show injury before the glomeruli. If the condition lasts long enough, swelling of the glomerular epithelium may be seen.

CHEMOTHERAPY OF INFECTIONS OF THE URINARY TRACT

Rantz and Keefer⁶⁴ discuss the curative effects of sulfanilamide in the light of the pathologic changes of pyelonephritis. In vitro, sulfanilamide was found to be both bacteriostatic and bactericidal in urine in concentrations in which it was neither in broth cultures. The maximum effects of sulfanilamide were obtained in vivo when the urinary concentration was 40 to 80 mg per hundred cubic centimeters. Its effects in vivo depend not only on its bactericidal effects in the urine but on its aid to the immunogenic mechanisms by which the deep structures of the kidney overcome infection. In judging the effectiveness of cure the decrease in sedimentation rate of the erythrocytes and the diminution in the number of leukocytes in the urine, as determined by the sediment count of Addis, give the most valuable evidence. The importance of the relief of urinary obstruction, if it exists, is stressed.

Alyea and Roberts⁶⁵ find the excretion of sulfanilamide and its derivatives in the urine is effected in the same manner as that of phenolsulfonphthalein. Studies of the action of the two substances in vitro and in vivo are not comparable, since the reaction of the tissues is more important than the bactericidal action in the urine. Mandelic acid was found to be satisfactory as an agent against infections with

62 Madding, G. F., Binger, M. W., and Hunt, A. B. Postpartum Urinary Suppression Resembling Bilateral Cortical Necrosis, *J. A. M. A.* **114** 1038 (March 23) 1940.

63 Penner, A., and Bernheim, A. T. Acute Ischemic Necrosis of the Kidney. A Clinicopathologic and Experimental Study, *Arch. Path.* **30** 465 (Aug.) 1940.

64 Rantz, L. A., and Keefer, C. S. Sulfanilamide in Treatment of Infections of the Urinary Tract Due to *Bacillus Coli*, *Arch. Int. Med.* **65** 933 (May) 1940.

65 Alyea, E. P., and Roberts, L. C. Chemotherapy in Nonspecific Infections of the Urinary Tract, *J. A. M. A.* **115** 1345 (Oct. 19) 1940.

Escherichia coli and with *Streptococcus faecalis*. Both sulfanilamide and sulfapyridine (2-[paraaminobenzenesulfonamido]pyridine) were effective in 81 per cent of patients with infections caused by *E. coli*. Seventy-five per cent of patients with staphylococcic infections were relieved by treatment with sulfapyridine, and 62.5 per cent of the patients whose infections were treated with sulfanilamide were cured. The responses to these drugs were rapid, a matter of two to three days. When the infections were complicated by other pathologic conditions, the patients did not respond as favorably. In general sulfanilamide is preferred to mandelic acid. High concentrations of the drug are not considered necessary. The authors recommend a dose of 1.8 Gm of sulfanilamide per diem with forcing of fluids, a regimen which was found to be fully as effective as 3 Gm per diem with restriction of fluids.

Cook⁶⁶ found that sulfanilamide, dimethyldisulfanilamide and sulfanilylsulfanilamide were most effective against gram-negative bacilli and beta hemolytic streptococci, and also against *Bacillus proteus*, since they are effective in alkaline urine. Staphylococci, micrococci and *Str. faecalis* were not affected by the drugs mentioned, with the exception of dimethyldisulfanilamide, which is not marketed because it may produce polyneuritis.

"The early experimental work with sulfapyridine showed little advantage in the treatment of infections of the urinary tract caused by the gram-negative bacilli or the streptococci. However it was of some value in the group caused by the staphylococci."

Sulfapyridine is of little value in treating infections caused by gram-negative bacilli and streptococci, but can be profitably used in staphylococcic infections. It is superior to sulfanilamide against gonococcic infections.

Sulfathiazole (2-[paraaminobenzenesulfonamido]thiazole) was effective against gram-negative bacilli, staphylococci and micrococci. The beta hemolytic streptococci do not respond so well to this drug, and *Str. faecalis* is destroyed in only 30 to 40 per cent of cases. With the organism last mentioned the reaction of the urine is of great importance. Helmholz found that at a p_H of 5.0 a concentration of 25 to 50 mg per hundred cubic centimeters was bactericidal, while at a p_H of 7.5 a concentration of 200 mg per hundred cubic centimeters was merely bacteriostatic.

When the renal function is low, Cook finds that azosulfamide (the disodium salt of 4-sulfamidophenyl-2''-azo-7'-acetylamino-1'-hydroxynaphthalene-3',6'-disulfonic acid) is useful, since it does not tend to injure the kidneys.

⁶⁶ Cook, E. N. Chemotherapy in Urology, J. A. M. A. **115**: 2079 (Dec. 14) 1940.

Toxic Effects—Lehr, Chrug and Antopol⁶⁷ find the renal excretory function is impaired by precipitation of acetylsulfamethylthiazole in the collecting tubules. In high concentrations degeneration of the parenchyma of the kidneys and the liver was observed. Stryker⁶⁸ described the formation of basophilic masses, consisting of acetylsulfapyridine, in the tubules, and also eosinophilic masses, which were regarded as protein extrusions from the tubular cells of the proximal convolution. These collect in the loop of Henle, causing obstruction and dilatation of tubules and Bowman's space. The concretions are due to excessive concentration and high acidity and may best be prevented by maintenance of greater diuresis and by alkalization. In discussing the hematuria resulting from the use of sulfathiazole in the treatment of pneumonia, Arnett⁶⁹ recommends a minimal intake of fluids of 3,000 cc and an output of 1,500 cc per diem. The drug is discontinued on the first appearance of hematuria or of lumbar pain. The urine should be examined daily for crystals of the acetylated drug and for erythrocytes. Loewenberg, Sloane and Chodoff⁷⁰ report the finding of concretions of sulfathiazole in the kidneys, ureters and bladder of patients in whom urinary abnormalities were not recognized during life.

PHYSIOLOGIC RELATIONS OF THE KIDNEY, NORMAL AND PATHOLOGIC

Formation of Urine and Renal Blood Flow—A well illustrated discussion of the minute and comparative anatomy of the kidney, with functional and morphologic correlations, has been prepared by Edwards⁷¹. Another paper, which articulates well with that of Edwards, is a discussion of the glomerular dynamics by Smith, Chasis, Goldring and Ranges,⁷² based on data concerning diodast and inulin clearances. The hydrostatic pressure in the glomerular capillaries is opposed by the oncotic pressure of the plasma proteins and by the pressure of filtrate within Bowman's capsule. When the control of the renal blood flow is effected entirely through the tonus of the efferent arterioles, the

67 Lehr, D., Chrug, J., and Antopol, W. Mechanism of Liver and Kidney Damage by Sulfamethylthiazole, *Proc Soc Exper Biol & Med* **45** 447 (Oct) 1940

68 Stryker, W. A. The Nature of the Renal Lesion with Sulfapyridine Therapy, *J A M A* **114** 953 (March 16) 1940

69 Arnett, J. H. Hematuria from Sulfathiazole Therapy in Pneumonia, *J A M A* **115** 362 (Aug 3) 1940

70 Loewenberg, S. A., Sloane, N. G., and Chodoff, P. Sulfathiazole Urinary Calculi in the Kidneys, Ureters and Bladder in the Absence of Marked Urinary Changes Following Sulfathiazole Therapy, *J A M A* **115** 2069 (Dec 14) 1940

71 Edwards, J. G. The Formation of Urine, *Arch Int Med* **65** 800 (April) 1940

72 Smith, H. W., Chasis, H., Goldring, W., and Ranges, H. A. Glomerular Dynamics in the Normal Human Kidney, *J Clin Investigation* **19** 751 (Sept) 1940

glomerular filtration rate remains nearly constant. The effects of the variations in the afferent flow may be calculated, but it is impossible at present for the experimenter to alter the afferent tone consistently and reproducibly.

The arteriovenous anastomoses described by Spanner⁷³ are believed by these authors⁷² to have no appreciable effects on the perfusability of the glomeruli, except to provide a shunt from artery to vein. Retrograde perfusion of the glomerular capillaries would be possible only during interruption of the arterial circulation. These anastomoses might also play a role in the survival of the aglomerular tubules sometimes found in cases of chronic nephritis.

Chesley and Chesley,⁷⁴ in discussing the mechanical principles of the renal blood flow as measured by the diodast and inulin clearances in women with hypertension and renal impairment, consider the effects of changes in the glomerular capillaries in the light of Poiseuille's law, which relates the length and diameter of capillary tubes and the viscosity and pressure of a liquid to the quantity of liquid flowing through the tubes.

Chasis, Redish and Erdmann⁷⁵ applied the clearance method to the determination of the blood flow of the individual kidney by using ureteral catheters and taking special precautions against leakage. Their procedure promises to be of value in detecting unilateral renal causes of hypertension.

Specific Gravity of Urine—Hayman, Shumway, Dumke and Miller⁷⁶ review the literature on specific gravity of urine from the time of Bright's paper to 1938. Hyposthenuria has been produced experimentally by reduction in renal mass, uranium poisoning, ureteral obstruction, denervation of kidneys and low protein diets. When dogs were subjected to subtotal nephrectomy, a concentrated urine could be formed under three conditions: (1) increased plasma proteins, (2) low blood pressure and (3) administration of sodium sulfate after deprivation of water. Under no circumstances could a urine of high specific gravity be obtained from a dog with tubular damage. The administration of solution of posterior pituitary led to an increase in the specific gravity of the urine in dogs with denervation of the kidneys, but this effect was not produced in hyposthenuria due to any other cause.

73 Spanner, R. Ueber Gefasskurzschlusse in der Niere, Verhandl. d. anat. Gesellsch. **45** 81, 1937.

74 Chesley, C., and Chesley, E. R. Renal Blood Flow in Women with Hypertension and Renal Impairment, J. Clin. Investigation **19** 475 (May) 1940.

75 Chasis, H., Redish, J., and Erdmann, A., Jr. Application of the Clearance Method to Determination of Unilateral Renal Blood Flow in Man, J. Clin. Investigation **19** 782 (Sept.) 1940.

76 Hayman, H. M., Jr., Shumway, N. P., Dumke, P., and Miller, M. Experimental Hyposthenuria, J. Clin. Investigation **18** 195 (March) 1939.

A study of the relation of the specific gravity of the urine to its composition by Price, Miller and Hayman ⁷⁷ revealed that urea, chloride, sulfate, phosphate, bicarbonate and creatinine exhibit additive effects on the specific gravity of aqueous solutions. An undetermined fraction of the total solids, amounting to 10 to 30 per cent, consists of organic acids and an unknown organic substance of low nitrogen content. Their findings indicate that calculations of the total solids excreted can be made from the specific gravity of the urine only in normal subjects who are taking a fixed diet.

Reaction of Urine—A practical investigation of the control of the reaction of the urine has been made by Bridges and Mattice ⁷⁸. This paper is of importance because such control is often essential to the proper conditions for chemotherapy of infections of the urinary tract or for the management of patients with urolithiasis. It was found that the urinary reaction cannot be consistently changed without regard to its natural trend. It has not been found possible to maintain a consistently alkaline urine. Temporary alkalinity has been best achieved by including cantaloupe in the diet. No other food was found to elevate the p_H of urine to such high levels (7.2 to 7.8). The most effective means of maintaining high urinary acidity was the substitution of cranberry juice for water. The effective use of acidifying drugs was found to be conditioned by the amount of water simultaneously claiming excretion. Concentration of the urine tends to be associated with increased acidity, and dilution, with increased alkalinity, yet the normal kidney is able to form a highly acid dilute urine and a definitely alkaline concentrated urine.

Fluctuations in the p_H of the urine during the day are related to the inconstancy of water excretion. Emotional states may influence the reaction.

The statement is made that in general the excretion of solids is most efficiently accomplished under conditions which yield an acid urine. In such urines fewer abnormalities are found than in neutral or alkaline urines.

Alving and Miller ⁷⁹ have improved the methods of determining inulin accurately in plasma concentrations as low as 5 mg per hundred cubic centimeters. The curve of the plasma concentration of inulin after injection of 10 Gm of this substance was plotted and the constancy of

⁷⁷ Price, J., Miller, M., and Hayman, J. M., Jr. The Relation of Specific Gravity to Composition and Total Solids in Normal Human Urine, *J. Clin. Investigation* **19**:537 (May) 1940.

⁷⁸ Bridges, M. A., and Mattice, M. Control of Urine Reaction, *Am. J. M. Sc.* **200**:84 (July) 1940.

⁷⁹ Alving, A. S., and Miller, B. F. A Practical Method for the Measurement of Glomerular Filtration Rate (Inulin Clearance), *Arch. Int. Med.* **66**:306 (Aug) 1940.

the inulin clearance revealed. The authors employ a 10 per cent solution of inulin and inject 100 cc at the rate of 10 cc per minute. Blood is taken at the midpoint of each period of urine collection. Using this method, Miller, Alving and Rubin⁸⁰ have found inulin clearance to be applicable to the study of patients with nephritis and hypertension, on the assumption that no inulin is resorbed in the tubules.

White,⁸¹ in a study of the diffusion equilibrium between the plasma and the cells of dog's blood, reaches the conclusion that there is a contribution of diodrast to the urine by the cells. White and Heinbecker⁸² obtained data concerning the relationship of diodrast clearance to the level of plasma iodine in dogs and to the surface area of the body. After hypophysectomy the plasma clearance and tubular output of dogs were about half normal.

White⁸³ found that when phlorhizin is given to dogs both the diodrast clearance and the glomerular filtration rate are lowered. The evidence indicates that these reductions are not due to diminution of the total renal plasma flow from which one would infer that diodrast clearance cannot be used for determination of renal blood flow in phlorhizinized animals.

Miscellaneous Papers—Toth⁸⁴ studied the formation of urine in dogs with anoxia. Oliguria was noted when gas mixtures low in oxygen were given to anesthetized dogs.

Steinitz,⁸⁵ using the endogenous creatinine clearance as a measure of glomerular filtration, studied the relation of the blood sugar to the "threshold" and the rate of resorption of dextrose.

Arkin and Popper,⁸⁶ measuring the glomerular filtration by the endogenous creatinine clearance, found resorption of urea progressively

80 Miller, B. F., Alving, A. S., and Rubin, J. The Renal Excretion of Inulin at Low Plasma Concentrations of This Compound, and Its Relationship to the Glomerular Filtration Rate in Normal, Nephritic, and Hypertensive Individuals, *J Clin Investigation* **19** 89 (Jan.) 1940.

81 White, H. L. Observations of the Effect of Diodrast in the Dog, *Am J Physiol* **130** 454 (Sept.) 1940.

82 White, H. L., and Heinbecker, P. Observations on Inulin and Diodrast Clearances on Renal Plasma Flow in Normal and Hypophysectomized Dogs, *Am J Physiol* **130** 464 (Sept.) 1940.

83 White, H. L. The Effects of Phlorhizin on Renal Plasma Flow, on Glomerular Filtration and on the Tubular Excretion of Diodrast in the Dog, *Am J Physiol* **130** 582 (Sept.) 1940.

84 Toth, L. A. Urine Excretion During Anoxia from Normal and Denervated Kidneys in Dogs With and Without Adrenal Glands, *Am J Physiol* **129** 532 (June) 1940.

85 Steinitz, K. Studies on the Conditions of Glucose Excretion in Man, *J Clin Investigation* **19** 299 (March) 1940.

86 Arkin, A., and Popper, H. Urea Reabsorption and Relation Between Creatinine and Urea Clearance in Renal Disease, *Arch Int Med* **65** 627 (March) 1940.

diminished in proportion to the severity of renal injury. In cases of the severest damage the urea clearance may exceed the creatinine clearance, indicating secretion by the tubular cells. Uremia due to excessive reabsorption of urea is regarded as an impossible condition.

Monke and Yuile⁸⁷ studied the clearance of hemoglobin in the dog. These authors found that the filtration of hemoglobin amounts to about 3 per cent of the filtrate and that a medium-sized dog may resorb about 2 mg per minute in the tubules. In these studies the endogenous creatinine clearance was used as a measure of filtration.

Renal function in gout was studied by Coombs, Pecora, Thorogood, Consolazio and Talbott⁸⁸. Most subjects with gout were found to show some evidence of renal damage and inability to concentrate urine. In the absence of severe renal impairment all but 10 per cent of the urates filtered were reabsorbed in the renal tubules. With severe impairment reabsorption was depressed and the clearance maintained. The drugs cinchopen and salyrgan diminished the tubular reabsorption, and thus increased the urate clearance. Colchicine was without effect on the urinary elimination of urates. Renal changes in gout are believed to be the result, and not the cause, of the metabolic disorder.

A statistical study of cases of renal infarction was made by Hoxie and Coggin⁸⁹. The most common causes were found to be bacterial endocarditis, auricular fibrillation, coronary occlusion and arteriosclerosis. They call attention to hemoglobinuria occurring in renal infarction. In 1 case, in which there was complete bilateral infarction, there were electrocardiographic changes resembling those described by Masters, Jaffe and Dack as characteristic of acute nephritis.

The myocardial degeneration associated with uremia is described by Gouley⁹⁰. Peculiar focal degenerations were found, which were more conspicuous when fresh and examined in the gross than they were under the microscope. The lesions differed from those usually associated with vascular occlusion. They were chiefly located in the subpericardial zone of the posterior and lateral walls of the left ventricle. Uremic pericarditis is believed to be a part of this process.

87 Monke, J. V., and Yuile, C. L. The Renal Clearance of Hemoglobin in the Dog, *J. Exper. Med.* **72** 149 (Aug.) 1940.

88 Coombs, F. S., Pecora, L. J., Thorogood, E., Consolazio, W. V., and Talbott, J. H. Renal Function in Patients with Gout, *J. Clin. Investigation* **19** 525 (May) 1940.

89 Hoxie, H. J., and Coggin, C. B. Renal Infarction. A Statistical Study of Two Hundred and Five Cases and Detailed Report of an Unusual Case, *Arch. Int. Med.* **65** 587 (March) 1940.

90 Gouley, B. A. The Myocardial Degeneration Associated with Uremia in Advanced Hypertensive Disease and Chronic Glomerular Nephritis, *Am. J. M. Sc.* **200** 39 (July) 1940.

News and Comment

American Diabetes Association—An organization known as the American Diabetes Association, Inc, has been formed, with the following officers Drs Cecil Striker, Cincinnati, president, Herman O Mosenthal, New York, and Joseph T Beardwood Jr, Philadelphia, vice presidents, Samuel S Altshuler, Detroit, secretary, William Muhlberg, Cincinnati, treasurer The honorary president is Dr Elliott P Joslin, Boston, and the honorary members are Drs Frederick G Banting† and Charles H Best, Toronto

According to the constitution and by-laws, the objectives of this new association are (1) to disseminate information relative to the diagnosis and treatment of diabetes by means of meetings, bulletins and publication of papers in scientific journals and through a central office, (2) to educate the laity in the early recognition of diabetes and in the realization of the importance of medical supervision, (3) to secure and coordinate the active cooperation of associated groups acceptable to the trustees in the educational and organizational phases of the association, (4) to make and publish statistical surveys of diabetes, (5) to encourage and support clinical, experimental, sociologic and statistical studies by means of grants, and (6) to encourage the adequate treatment of diabetes and the establishment of summer camps for children

Committees are now engaged in developing a membership list and a program for a one day clinical session in Cleveland, at the Hollenden Hotel, on Sunday, June 1, at 1 30 p m

† Deceased

Book Reviews

Injection Treatment of Hernia, Hydrocele, Ganglion, Hemorrhoids, Prostate Gland, Angioma, Varicocele, Varicose Veins, Bursae and Joints
By Penn Riddle, B S, M D, F A C S Price, \$5 50 Pp 290, with 153 illustrations Philadelphia W B Saunders Company, 1940

A practical book on injection treatment undoubtedly is timely. Riddle has had considerable experience with the operative treatment of various disorders as well as with the injection method of treatment of the same disturbances, and for this reason he is peculiarly suited to the evaluation of both methods of treatment. He states the belief that the injection treatment is not applicable in all cases, and he strives to show under what conditions it is, in his experience, indicated.

In this readable book, which is attractively arranged and well illustrated, Riddle discusses the indications and contraindications for the injection treatment of hernia, hydrocele, ganglion, hemorrhoids, conditions of the prostate gland, angioma, varicocele, varicose veins, bursae and diseases of the joints. The anatomic considerations involved and the technic of injection for the treatment of these disturbances are well described and illustrated, and the applicability of the various sclerosing solutions is discussed with recommended dosages.

Naturally, the greater share of the book is concerned with hernia, varicose veins and hemorrhoids, and although the physician personally may be opposed to the use of sclerosing solutions in the treatment of hernia or hemorrhoids, the reader cannot but be impressed with the fairness of the author in his discussion of these controversial subjects.

Riddle states the belief that "In general any small indirect inguinal hernia that can be reduced and maintained in a state of complete reduction while the patient is ambulatory can be successfully treated by the injection method." He states further, "No hernia with a ring over 2 cm in diameter should be treated unless the patient is impressed with the fact that a cure is very doubtful though improvement may follow." Although the author does not commit himself in regard to the cure of direct hernias by the injection method, he does state that "Very small hernias, in non-obese subjects, may be markedly improved." He recommends surgical intervention for femoral hernia and umbilical defects more than 2 cm in diameter. He states the opinion that the "treatment of large external inguinal rings (potential hernias) offers a great field for the application of the injection method of treatment."

The chapters on the treatment of varicose veins are well written, and the author's experience coincides with the views of most of the authorities in this country on this subject.

Riddle advises that "Only simple internal hemorrhoids are suitable for the injection treatment." He is "of the opinion that most anal fissures and fistulae are true varicose ulcers, and oftentimes anal pruritus is merely static eczema, the result of improper venous return from the anus, rectum and perineum."

This book should prove valuable and interesting to any physician, irrespective of his field of practice.

The Calcified Pineal Gland By Dr W Bergmann Pp 89, with illustrations Assen Van Gorcum & Comp, N V, Amsterdam, 1940

This short monograph includes approximately 70 pages of discussion, illustrated by a few tables, figures and graphs and by one photograph of a roentgenogram. The subject is introduced by a brief description of the embryologic, the histologic and the anatomic characteristics of the pineal gland. The author then considers calcification of the gland, methods of determining the position of the gland from roentgenograms, forms the calcification may assume and structures which may be

confused with the pineal body. The incidence of calcification in the various decades of life is determined in 1,200 cases.

The remainder of the book is devoted to the physiology and pathology of the pineal gland and to the significance of a calcified gland in diagnosis and therapy. Quotations from the literature are incomplete, and results are stated without evaluation of the research involved. Many opinions expressed are unsupported by scientific data. The clinical manifestations ascribed to disease of the pineal gland are unwarranted by the material presented. The author's interpretation of the significance of calcification of the pineal gland has resulted in an uncritical appraisal of previous investigative work. The book is poorly organized, and in many instances ideas are not clearly expressed. The section on the incidence and localization of the calcified pineal gland may be of interest to the neurologist and roentgenologist.

Compendium of Regional Diagnosis in Lesions of the Brain and Spinal Cord By Robert Bing, Professor of Neurology, University of Basel, Switzerland. Translated and edited by Webb Haymaker, Assistant Clinical Professor of Neurology and Lecturer in Neuro-anatomy, University of California. Eleventh edition. Price \$5.00, cloth. Pp 292, with 125 illustrations, 27 in color and 7 plates. St. Louis: C. V. Mosby Company, 1940.

This compendium, the first edition of which appeared in 1909, needs no introduction to neurologists, although it was written with the purpose of serving any physician or surgeon who might be called on to localize a pathologic process affecting the central nervous system. Although the present edition is larger than those that preceded it, the author has succeeded, in the main, in presenting a reputedly complicated subject simply, accurately and comprehensively.

In part I he discusses the localization of lesions of the spinal cord, first in the transverse plane and then in the longitudinal plane. The anatomy, physiology and semeiology are taken up in turn.

In part II the localization of cerebral lesions is approached in a similar manner. He first considers the brain stem, next the cerebellum and finally the cerebrum, basal ganglions and hypophysis. At the end of each part roentgenologic aspects of diagnosis and localization are discussed briefly. The work is adequately illustrated, and the illustrations are satisfactorily labeled. The print is large and clear, the paper of good quality, the translation well done and the index complete and accurate.

The hope of the author that this edition of his compendium may serve a purpose useful to the neurologist and to the surgeon and general practitioner will undoubtedly be realized. The book may be recommended unhesitatingly as an eminently satisfactory treatment of this subject.

Chemotherapy and Serum Therapy of Pneumonia By Frederick T. Lord, M.D., Clinical Professor of Medicine, Emeritus, Harvard Medical School, Member of the Board of Consultation, Massachusetts General Hospital, Elliott S. Robinson, M.D., Ph.D., Director, Division of Biologic Laboratories, Massachusetts Department of Public Health, and Roderick Heffron, M.D., Medical Associate, the Commonwealth Fund, formerly Field Director of the Pneumonia Study and Service, Massachusetts Department of Public Health. Price, \$1.00. Pp 174, with illustrations. New York: Commonwealth Fund. London: Oxford University Press, 1940.

This book, though brief, represents an attempt on the part of its authors to evaluate the present status of chemotherapy and serum therapy in the treatment of pneumonia, based on the experience of a comparatively large and active public health service, especially in Massachusetts.

It attempts, however, to deal with the subject, namely, pneumonia, with reference to the entire problem of the management of this infection. It treats in its

subject matter the etiology, the diagnosis, the recognition of types of pneumonia, the immunity factors and the prognosis, in addition to its primary purpose, namely, chemotherapy and serum therapy. For the reason that it deals with the entire problem this book should be of considerable interest to the general practitioner, although its value as a reference book is questionable.

The authors attempt to show, although inconclusively, that the identification of the inciting organism is of great importance. No convincing evidence is presented which would indicate any advantage in the combined use of chemotherapy and serum therapy in the treatment of pneumonia. On the other hand, evidence is presented which would favor the combined use of serum and chemotherapy in the treatment of bacteremia due to *Diplococcus pneumoniae*. The authors fail, however, to take into account the financial aspects of the problem, which must be reckoned with in the employment of the two types of therapy in private practice.

Essentials of the Diagnostic Examination By Dr John B Youmans, Associate Professor of Medicine and Director of Postgraduate Instruction, Vanderbilt University Medical School. Price \$3.00. Pp XVI + 417, with 36 illustrations and 24 tables. New York: Commonwealth Fund. London: Oxford University Press, 1940.

This is a dapper little volume, well printed on thin paper and of such size, shape and weight as to conveniently fit into one's pocket or bag. It is unpretentious. The essentials of the diagnostic examination are described, history taking in 16 pages, physical examination in 142 pages and laboratory tests in the remaining 218 pages.

On first sight this spacing of the material may appear unusual and as if undue emphasis was placed on the laboratory tests and too little on history taking. Such is not the case. Nobody can tell how to take a good history beyond suggesting bare outlines. The technic of physical examination is easier to describe, and certainly the author outlines the methods of physical examination in a satisfactory manner, including sensible, easily understandable description of neurologic examination. The laboratory manual part of the book describes ordinary clinical laboratory work and methods with clarity and detail.

On the whole, the new "Essentials of the Diagnostic Examination" is a good 1940 model. Every physician ought to have an up-to-date booklet of this character as part of his standard equipment, in constant use and as well thumbed as any priest's book of prayers. This particular volume contains few errors, is handy and, above all, is put together by a competent clinician thoroughly familiar with all of which he writes. It deserves a successful life.

The Fundamentals of Internal Medicine By Wallace M. Yater, M.D. Price, \$9.00. Pp 1,021, with 255 illustrations. New York: D. Appleton-Century Company, Inc., 1940.

The number of new textbooks of medicine to appear in recent years indicates that no really satisfactory one volume treatise is available, the subject has become so large and abstruse that the old fashioned descriptive "practice" is now pretty much out of order. Discussions usually center on the question of whether one man can write the ideal medical textbook or whether it should be compounded out of the essays of a group of authorities and whether it should be encyclopedic or more especially designed to bring out some homogeneous point of view for the student. These problems are not solved, nor is there ever again likely to be a wholly satisfactory one volume textbook of medicine. That has gone with the coming of television, the airplane and the radio. The tempo of medicine is too fast!

Dr Yater's book represents an excellent and successful attempt to state in simple, concise and even dogmatic terms the essentials of internal medicine. This is a somewhat new type of book, not written in the usual textbook style, it is a supersynopsis. Some of the discussions of important matters are alarmingly brief.

To pick an example at random, in the section on treatment of exophthalmic goiter the entire problem of iodine preparation for operation is dealt with in two and one-third lines. As much or more space is given to Bednar's aphthae, Riga's disease and torus palatinus. There are many excellent illustrations.

The Pathology of Internal Diseases By William Boyd. Third edition. Cloth. Price \$10. Pp 874, with 353 engravings and 4 colored plates. Philadelphia: Lea & Febiger, 1940.

Any medical textbook noted for its readability is unusual, but a textbook on pathology that is easy to read is unique. The reviewer of the first edition (*ARCH INT MED* 47:988 [June] 1931) made the following comment: "If one opens the book at any of the important chapters, one is immediately engrossed in the subject matter." It is unfortunate that the same remark cannot be made about more books in the realm of medical literature.

The third edition is much the same as the two previous ones. As the author states, "Much new material has been added and a number of sections have been rewritten, but the size of the book has not been increased owing to deletion of older material and to the use of small type for sections of minor importance." That a third edition is necessary in the space of nine years speaks well for activities in the field of pathology which is rapidly becoming a broader field of pathologic physiology.

The reviewer, having a special interest in hematology, was particularly concerned with the treatment of this subject. The section was excellently done in general, and the reviewer's only criticism is the omission of a few pertinent articles in the recent literature. In regard to another section, that on the gastrointestinal tract, a discussion of the pathologic changes of appendicitis might be included. The appendix remains in the realm of internal medicine until it is removed by the surgeon.

The book is definitely to be recommended and should be the wedded companion of any general text on internal medicine.

Biological Symposia Edited by Jaques Cattell. Price, \$2.50, postpaid. Pp 238. Lancaster, Pa.: The Jaques Cattell Press, 1940.

At the Richmond meeting of the American Association for the Advancement of Science, in December 1938, a day was devoted to general discussion of "The Cell Theory: Its Past, Present and Future." The occasion was a celebration of the one-hundredth anniversary of this theory as propounded for plant cells by Schleiden and applied to animal cells by Schwann. However, as was emphasized by each of the speakers, the ideas exploited by Schleiden and Schwann involved an erroneous conception which had been developed by other men, long before either Schleiden or Schwann appeared on the scene. The celebration consisted, therefore, of putting Mr. Schleiden and Mr. Schwann in their proper places. The report of this discussion makes reading which is both entertaining and enlightening.

Two other symposia are contained in the volume, one on "Mating Types and Their Interactions in Infusoria," the other on "Chromosome Structure." They are somewhat technical for the average physician, but help to form a related series and undoubtedly add to the value of the volume.

Practical Bedside Diagnosis and Treatment By Henry Joachim, M.D. Price, \$7.50. Pp 828. Springfield, Ill.: Charles C. Thomas, Publisher, 1940.

This book is pleasantly written by a man who obviously has a wide clinical background. It is hard to see, however, just what it adds to any one of a number of standard textbooks already in use. The descriptions of disease are good but sketchy, and much space which could better be used is devoted to rare or unimportant conditions. The outlines of treatment are sound but often not given in enough detail to help the inexperienced.

VASCULAR ALLERGY

PATHOGENESIS OF BRONCHIAL ASTHMA WITH RECURRENT PULMONARY INFILTRATIONS AND EOSINOPHILIC POLYSITROSITIS

JOSEPH HARKAVY, M D

NEW YORK

In the pathogenesis of bronchial asthma mediated by specific hypersensitiveness, hereditary predisposition, as well as the immunologic mechanism, frequently plays an important role. This is especially common among atopic patients. The immunologic mechanism is regarded as involving an antigen-antibody reaction on or within certain cells or tissues designated as shock organs. These organs are likewise usually subject to hereditary influences. The particular site of the allergic reaction, whether the epithelium, the smooth muscle or the endothelium of blood vessels, has been subject to a great deal of controversy. It is the purpose of this paper to review this phase of the problem and to indicate that the vascular apparatus plays a basic role in the production of altered tissue reactivity in man.

A number of arguments support this hypothesis.

According to Lewis¹ and Dale² the antigen-antibody interaction is supposed to result in the liberation of a histamine-like substance which leads to increased vascular permeability and consequent edema. This edema is considered to be responsible for the production of the clinical symptoms of allergy. The initial implication of the endothelium of blood vessels rather than the smooth muscle in this effect seems to be obvious. Moreover, sensitization of smooth muscle of human origin like the sensitization which exists in lower animals has not been demonstrated. Since, therefore, the blood vessels appear to be the primary site of the allergic reaction, it may be reasoned that any organ in the body may

From the Medical Services of the Mount Sinai and Montefiore Hospitals.

Read at the annual meeting of the American Society for the Study of Allergy, St. Louis, May 15, 1939.

1 Lewis, T. *The Blood Vessels of the Human Skin and Their Responses*, London, Shaw & Sons, Ltd., 1927.

2 Dale, H. H. On Some Chemical Factors in Control of Circulation, Croomian Lectures, Brit. M. J. **1** 1093, 1929, *Lancet* **1** 1179, 1233 and 1285, 1929.

	Case 1 F B , 21	Case 2 S G , 42	Case 3 L G , 48	Case 4 D Z , 26
History	Mother, hay fever, sister, hives, colds since 1932, cough and expectoration	Colds for many years, cold in February 1936	Cough in 1936, asthma and hay fever in family	Epidermophytosis during summer 1937, injections of chorionic gonadotropin (antuitrin S) and oral administration of pituitary gland
Sinal disease, roentgenogram positive	Antrums and sphenoid sinuses	Pansinusitis	Polypoid ethmoiditis	Involvement of right antrum and sphenoid sinus
Bacteriologic study of sinuses	Cultures of washings positive for Staph aureus haemolyticus			
Asthma	Moderate	Severe, recurrent from 1936 to 1939	Present from 1936 to 1938	None, cough and bloody expectoration
Chest	Recurrent pulmonary infiltrations, ten recurrences from 1932 to 1939	Recurrent infiltrations on two occasions, March 1937 and December 1937	Oct 21, 1938, mottled infiltration in lower lobes of both lungs, Nov 19, pulmonary infiltrations throughout both lungs interstitial in character	Oct 3, 1937, faint infiltration in lower lobe and more dense infiltration in middle lobe of right lung Oct 8, confluent infiltration throughout both upper lobes, interstitial infiltrations in both upper lobes suggestive of interstitial pneumonitis, Nov 19, resolution of lungs
Sputum	Eosinophils present	Eosinophils present	Eosinophils present	
Bacteriologic study of sputum		Cultures positive for pneumococci, streptococci, Vincent's spirillae and fusiform bacilli	Cultures positive for Str haemolyticus, Str viridans and Micrococcus catarrhalis	Cultures positive for yeast, Str viridans, Staph aureus B, M pharyngis siccus
Blood count *	W B C (minimum) 7,600, (maximum) 32,000, H B 66%	W B C 16 500 R B C 4,160,000, H B 90%	W B C (minimum) 16,000, (maximum) 24,300 R B C 5,800,000, 3,570,000, color index 0.7, H B 63%	W B C (minimum) 14,500, (Oct 9, 1937) 21,800, culture sterile
Eosinophils, %	17 to 54	63	26 to 47	39, 52 and 65
Cutaneous reactions	Positive reactions to foods and to pollens of trees, timothy and ragweed	Positive reactions to ragweed, timothy and dust	Slight reactions to various foods, dust and tobacco	Positive reactions to egg, beef, lamb, rice, mustard, pepper, plantain, feathers and the like
Cardiac involvement	Not studied	Not studied	Nov 4, 1938, T wave in lead I semi inverted and T wave in leads II and III inverted, Nov 17, sinus tachycardia present in Q wave in lead III T wave in lead III inverted, insufficient evidence of myocardial involvement	Oct 9, 1937, left ventricular preponderance in Q wave of lead I present, suggesting hypertrophy of left ventricle, T wave in lead III inverted, T wave in lead IV isoelectric and may be abnormal changes in the deflections and amplitude in T waves apparent in repeated electrocardiograms, on Nov 24, 1937 T waves in leads I, II and lower lead IV normal

* The following abbreviations are used W B C, white blood cells, H B, hemoglobin concentration, and

Recurrent Pulmonary Infiltrations and Eosinophilic Polycystosis

Case 5 F H , 21	Case 6 P D , 41	Case 7 B S , 32	Case 8 M B , 88
No family history of allergy, colds since infancy, eczema and cough since age of 16, rhinorrhea since July 1934	Ragweed hay fever for many years, sinusitis for 8 years, operation in 1933 followed by relief for some time	No family history of allergy, cold December 1937, cough	Exposure in ice box in August 1931 followed by cold, chill and pain in right side of chest
Bilateral maxillary and ethmoid sinusitis	Pansinusitis	Sinusitis, polypectomy, polypoid sinusitis, clouding of all sinuses shown in roentgenogram taken April 5, 1938	Pansinusitis, recurrent attacks
Cultures of washings positive for Staph aureus, Str viridans and Staph albus	Cultures of washings positive for Staph aureus and Staph citreus		
Severe	Severe, recurrent since 1932	In 1937 asthmatic bronchitis for 6 months, asthma clearing in summer, recurrent attacks relieved by epinephrine, asthma and cough severe and continuous at time of readmission to hospital July 9, 1938	Severe, recurrent
Asthma in January 1937, temp 104 F, roentgenogram of chest negative, although signs of broncho pneumonia found over base of left lung, May 18, 1938, infiltration in lower or middle and upper lobes of left lung, Aug 16, irregular infiltration in lower lobe of left lung, March 20, 1939 roentgenogram normal, heart normal, April 11, pulmonary infiltration in upper lobe of left lung, May 18, 1939, infiltration in upper lobe of right lung, pleural exudate	March 8, 1935, areas of interstitial infiltration in lower lobe of right lung, July 22, 1935, inflammatory reaction of left hilar lymph nodes, which show marked enlargement, Aug 16, 1935, disappearance of root shadow	Feb 14, 1938, roentgenogram of chest, distinct exaggerations of pulmonary markings at bases of both lungs and linear shadows over both lungs, probably due to residual pleuritic thickening	July 9, 1934, roentgenogram, marked hilar fibrosis, organized productive infiltrations in both central pulmonary fields, May 13, 1935, bilateral hydrothorax, recurrent pulmonary infiltrations in 1935 and 1936, subsidence in 1937
Eosinophils present	Greenish, mucoid, containing numerous eosinophils	Eosinophils present	Eosinophils present
W B C (minimum) 18,000, (maximum) 30,000 to 40,000, marked eosinophilia of bone marrow revealed by puncture	W B C (minimum) 18,300, (maximum) 23,000, anemia, H B 50%	W B C 14,000 to 18,000, eosinophilia (eosinophils 11.2%, eosinophilic myelocytes 6.2%) of bone marrow revealed by puncture	Cultures positive for pneumococci, diphtheroids, gamma hemolytic streptococci, Staph albus and Staph aureus
35, 38 and 50	30, 50, 60 and 84	30 to 40	7 to 39
Essentially negative	Positive reactions to ragweed, dust, tuna fish, peas and Staph aureus vaccine	Negative	Negative
July 1937, sinus tachycardia (rate 115), T wave in lead II, low T wave in lead III semi inverted Oct 7, 1938, pericarditis, sinus tachycardia (rate 110), QRS complex notched in lead II, Q wave present lead III, T waves isoelectric in all leads, venous pressure 16.25 cm after pressure on upper right quadrant of abdomen, pressure in right jugular vein 23.5 cm, rising to 31.5 cm, normal again on Oct 30 April 11, 1939, sinus tachycardia (rate 130), QRS complexes notched in lead II, high voltage in P wave and low in T waves in leads I II and III suggestive of involvement of ventricular muscle	July 21, 1935, sinus tachycardia (rate 105), right ventricular preponderance, large P waves, slurring of QRS complexes, T waves in leads II and III inverted, hypertrophy of right ventricle with myocardial involvement indicated by abnormalities, Oct 2, QRS complex low in lead I, T wave in lead II upright, T wave in lead III isoelectric, Nov 18, sinus tachycardia, no other changes	February 1938, pericardial friction rub in 4th left intercostal interspace, cardiac enlargement to right and left, studies of circulation time indicative of right sided heart failure, fluoroscopic examination, adhesive pericarditis and mediastinitis, enlargement of right ventricle but not of left visible in roentgenogram, Feb 10, 1938, sinus tachycardia (rate 115), QRS complex slurred and of moderately low voltage, T waves in leads I II and IV inverted, changes indicative of involvement of ventricular muscle	July 9, 1934, right axis deviation, low voltage changes of T waves suggestive of myocardial damage, March 9, 1935, fast rate, right axis deviation, low voltage, first stage of auriculoventricular block, pericardial effusion, enlargement to right and left, progressive cardiac failure due to constrictive pericarditis

R B C , red blood cells

Signs and Symptoms in Eight Cases of Bronchial Asthma with Recurrent

	Case 1 F B 21	Case 2 S G , 42	Case 3 L G 48	Case 4 D Z , 26
Serous membranes	Two attacks of pleurisy with effusion	Bilateral pleural effusion, 900 cc of amber fluid on thoracentesis		Effusions in bases of both lungs, consisting of hemorrhagic fluid showing 95% of eosinophils, culture of fluid sterile
Cutaneous lesions	None	None	None	Necrosis of skin in Scarpa's triangle of right thigh
Biopsy of skin	Negative	Negative	Negative	Oct 11, 1937, biopsy of lesions in Scarpa's triangle, acute diffuse inflammation with eosinophilia
Extremities	Normal	Normal	Normal	
Complications	None	None	None except for mild arteriosclerosis of fundi	
Result	Patient well	Patient well	Patient well	Patient well

become a shock tissue if the blood vessels supplying it have become sensitized. The simplest example of this is urticaria or eczema due to food hypersensitiveness, in which the skin becomes a shock organ by virtue of sensitization of the blood vessels which supply it. Further evidence of sensitization of blood vessels as such has been presented in my demonstration of tobacco allergy in thromboangitis obliterans, varying forms of migrating phlebitis and certain types of angina pectoris in young persons with or without disease of the coronary arteries. Biopsies of skin taken from areas of cutaneous reaction to tobacco in persons with such conditions showed typical perivascular infiltrations of eosinophils and edema. Similar findings by Sulzberger³ have confirmed these observations. The experimental production of gangrene of the toes of male rats following intraperitoneal injection of denicotinized tobacco extracts by Friedlander, Silbert and Laskey⁴ and by Harkavy,⁵

³ Sulzberger, M. B. Recent Immunologic Experiments in Tobacco Hypersensitivity, *Bull New York Acad Med* **9** 294, 1933

⁴ Friedlander, M., Silbert, S., and Laskey, N. Toe Lesions Following Tobacco Injections in Rats, *Proc Soc Exper Biol & Med* **34** 156, 1936

⁵ Harkavy, J. Tobacco Sensitization in Rats, *J Allergy* **9** 275, 1938

Pulmonary Infiltrations and Eosinophilic Polysclerosis—Continued

Case 5 F H , 21	Case 6 P D , 41	Case 7 B S , 32	Case 8 M B , 35
Pericarditis and mediastinitis pleuritis on the right side	Ascites 10,500 white cells per cubic centimeter, with 85% eosinophils, culture of ascitic fluid sterile pleurisy at base of right lung	Ascites cells in ascitic fluid 80% eosinophils, culture sterile	Bilateral pleural recurrent effusion with eosinophilia culture of fluid sterile, ascites present
Negative	Negative	Urticaria, purpura	Urticaria angioneurotic edema purpura
Polvarthritis, lasting about a week	Numbness and weakness of legs myelodisculitis, palsy on left side of face, polyneuritis	Subepidermal edema, diffuse perivascular and perineural infiltration with eosinophils, no vascular lesion, infiltration of purpuric lesion with eosinophils	Biopsy of nodule in 1936, subacute inflammation limited to perivascular tissues of small arteries" typical periarteritis nodosa in another section from same nodule
	Acute abdominal pain and shock due to mesenteric occlusion, followed by peritonitis stools positive for blood, temp 104 F, disappearance of eosinophils from blood and peritoneal fluids, localized abdominal abscess due to perforation of intestine, aspiration and drainage of abscess, localization followed by improvement, red blood cells in urine on Aug 9, 1935	Urticaria and purpura over ankles, legs and arms, polyneuritis	Polvarthritis in 1936, polyneuritis, purpura on feet and ankles edema of feet
		Temperature 101 to 102 F, acute abdominal pain ascites, enlarged liver, distention of abdominal veins, icterus	Generalized lymphadenitis chronic lymphadenitis with eosinophilia shown on biopsy of lymph node development of nodules on forearm showing periarteritis nodosa amyloidosis of liver, with 100% retention of congo red, hypoproteinemia, albuminuria peripheral edema with out hypertension
Patient discharged with some improvement, Dec 24, 1935, recurrences of mild asthma after January 1939, at present asthma severe and patient in hospital	Asthma improved for a while recurrence in November 1936, asthma still present	Constrictive pericarditis death from cardiac failure	Constrictive pericarditis death after acute lobar pneumonia due to Pneumococcus type XIX

as well as the demonstration that these animals had been sensitized to tobacco, lends added support to the concept of involvement of blood vessels in the allergic response

The present report deals with other forms of vascular sensitization as manifested in a group of 8 patients in whom with a single exception asthma was the cardinal symptom. The object of this study is to demonstrate that the asthma was but one of the expressions of varying degrees of underlying vascular allergy and appeared concurrently or alternately with involvement of other tissues subject to the same allergenic stimulation

CLINICAL FINDINGS

A synopsis of the signs and symptoms manifested by the patients under investigation is presented in the table. As intimated previously the initial symptom, with 1 exception, which sent these patients to the hospital was severe bronchial asthma. Inquiry into their past revealed the existence of a family and a personal history of allergy in 2 and 4 patients, respectively. Investigation by means of intradermal cutaneous tests of the possible agents responsible for the attacks disclosed positive reactions to pollens and foods in 5 of the 8 patients (cases 1 2. 3 4

and 6) These reactions were found to be clinically significant only in 3 (cases 1, 2 and 6) The major etiologic role in the causation of the presenting symptoms in the majority of the patients was attributed to bacterial allergy emanating from chronically infected sinuses Coincidentally with the asthmatic attacks there appeared interstitial pulmonary infiltrations, abnormal electrocardiographic changes⁶ (figs 1, 2 and 3) and pleural effusions of eosinophils in close succession in 6 of the patients These signs were reversible and disappeared with the termina-

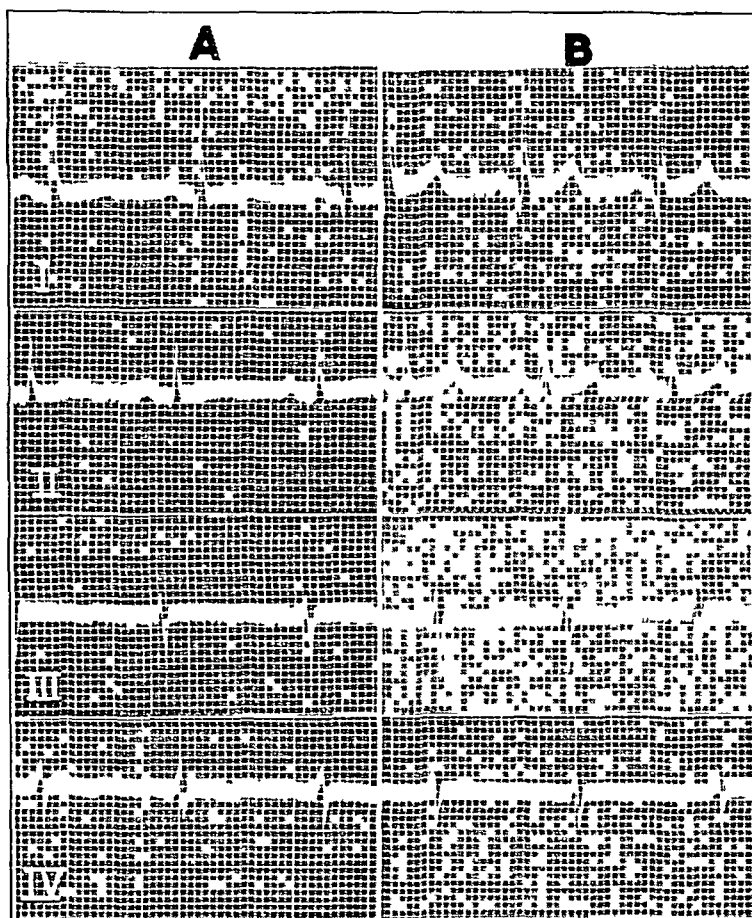


Fig 1 (case 4)—*A*, electrocardiogram made Oct 23, 1937 The T waves are low in the standard leads and inverted in lead IV *B*, electrocardiogram made November 16 The T waves are normal in the standard leads and low in lead IV

tion of the asthmatic seizures, only to recur with their recrudescence (figs 4 through 6) In the patient (case 4) who did not have asthma, in addition to the pleuropulmonary infiltrations and electrocardiographic changes, there appeared swelling of the elbow and a hemorrhagic necrotic lesion in Scarpa's triangle, all of which disappeared with recovery of the patient within a period of three months Biopsy of material from the necrotic lesion showed an inflammatory reaction with perivascular infiltration of eosinophils (fig 7)

⁶ In cases 1 and 2 the patients were not studied electrocardiographically

In the course of an asthmatic attack in case 5, there developed, in addition to the pulmonary infiltrations and electrocardiographic deviations, involvement of the pericardium. Concurrently with the acute pericarditis, which prevailed for about three weeks, the asthma subsided, while urticaria and fugitive polyarthritis appeared and remained about a week. These symptoms would be suggestive of rheumatic fever.

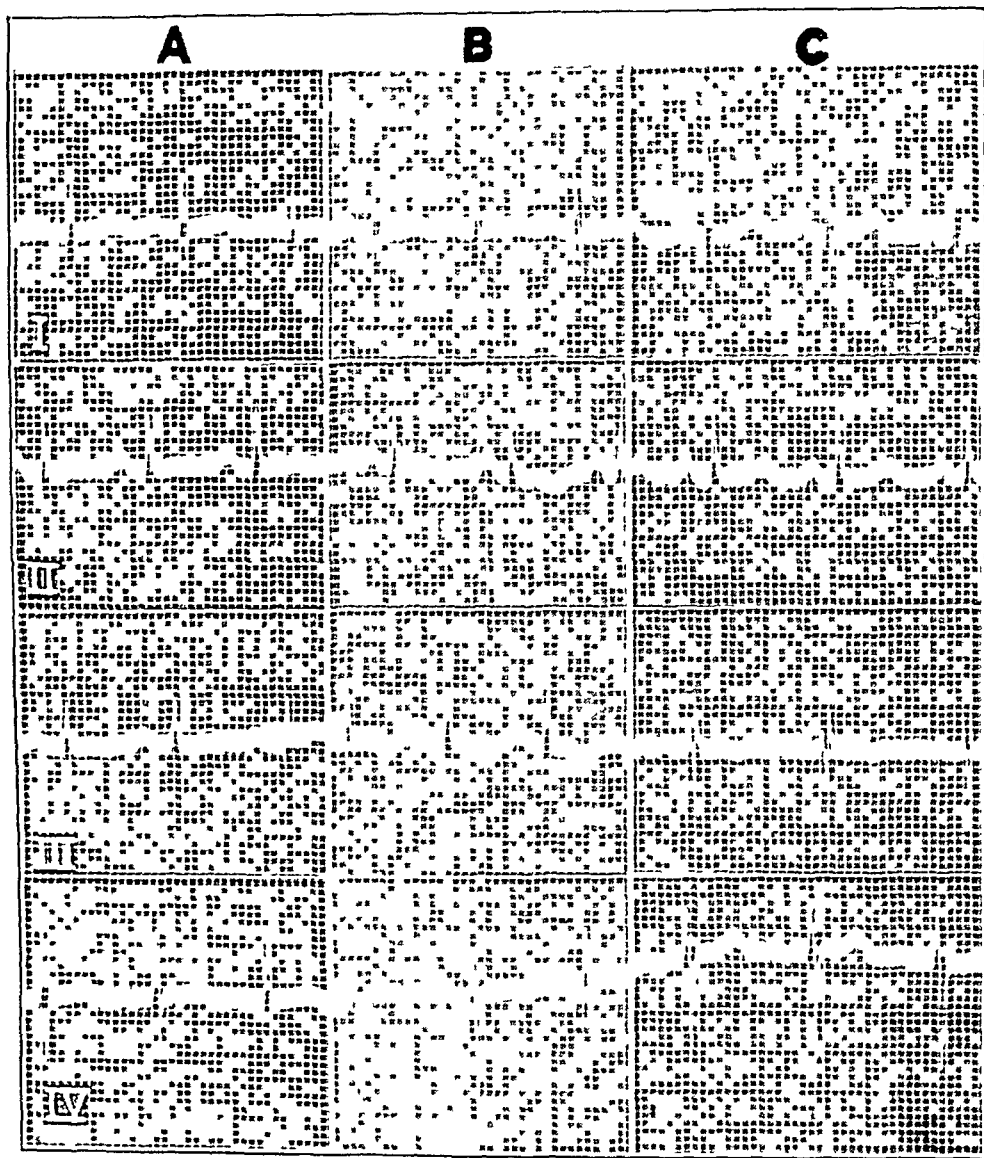


Fig 2 (case 5)—*A*, electrocardiogram made July 1, 1937, during an attack of asthma. The T waves are isoelectric in leads II and III, and the QRS complex is notched in lead II. *B*, electrocardiogram made Nov 14, 1938, at the termination of an episode of acute pericarditis with asthma. The T waves are inverted in leads I, II and III, and the voltage of the QRS complex is lowered. *C*, a normal electrocardiogram made April 11, 1939, showing left axis deviation.

were it not for the high degree of eosinophilia in the blood which persisted throughout and the subsequent return of asthma. Recurring attacks of the latter during the past three years were invariably associated with pulmonary infiltrations and electrocardiographic deviations.

There has been no return of pericarditis, and the cardiac outlines have remained within normal limits as far as can be determined by roentgen ray examination

In case 6, along with the asthma, pulmonary lesions and electrocardiographic changes, there appeared eosinophilic peritonitis and polyneuritis, which also affected the left side of the face The polyneuritis in conjunction with the other phenomena suggested the possibility of hyperergic vascular disease of the nature of periarteritis nodosa

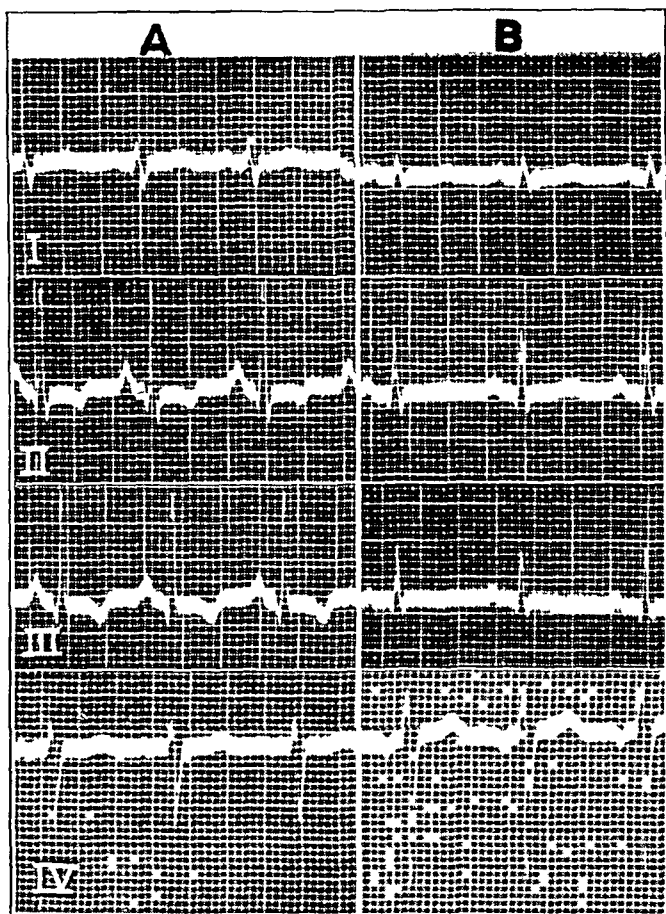


Fig 3 (case 6) —*A*, electrocardiogram made Aug 1, 1935, while bronchial asthma was present There is right axis deviation, the P waves are large, the QRS complex is slurred in lead I, and the T waves are inverted in leads II and III *B*, electrocardiogram made October 2 There is no right axis deviation, and the T waves are upright but low, reverting toward normal

Although no direct proof of this was available in biopsies of muscle and skin, a sudden onset of acute abdominal pain and bloody stools in the course of the eosinophilic peritonitis indicated a mesenteric thrombosis on a vascular basis The infarction of a segment of intestine which followed caused localized suppurative peritonitis The affected area was drained and the patient recovered During this episode the eosinophilia



Fig 4 (case 1)—*A*, on April 7, 1934, roentgen ray examination revealed bilateral interstitial infiltration of the lungs. On May 4 the condition of the lungs was normal, and on May 31 there was recurrence of the same type of infiltration. *B*, on Feb 1, 1937 there was marked infiltration of the apical portions of the lower lobes and the lower portion of the upper lobes of the lungs. On March 4 the lungs were clear.

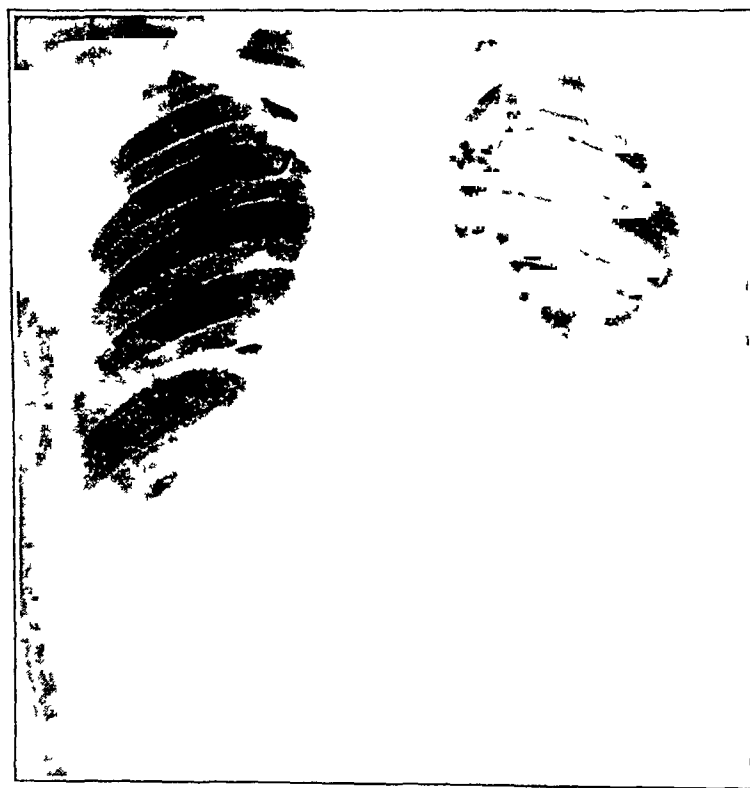


Fig 5 (case 2)—On March 12, 1937 distinct interstitial infiltrations were present in both lungs but were more marked in the right than in the left. Bilateral pleural effusion was present April 3, and by May 2 the effusion was absorbed.



Fig 6 (case 8)—*A*, on March 17, 1937 there was diffuse interstitial infiltration, with an area of consolidation in the upper lobe of the left lung and a small pleural effusion. The heart was enlarged to the right. *B*, by April 20 there was almost complete absorption of pulmonary infiltrations and the effusion was bilateral. The cardiac shadow was enlarged.

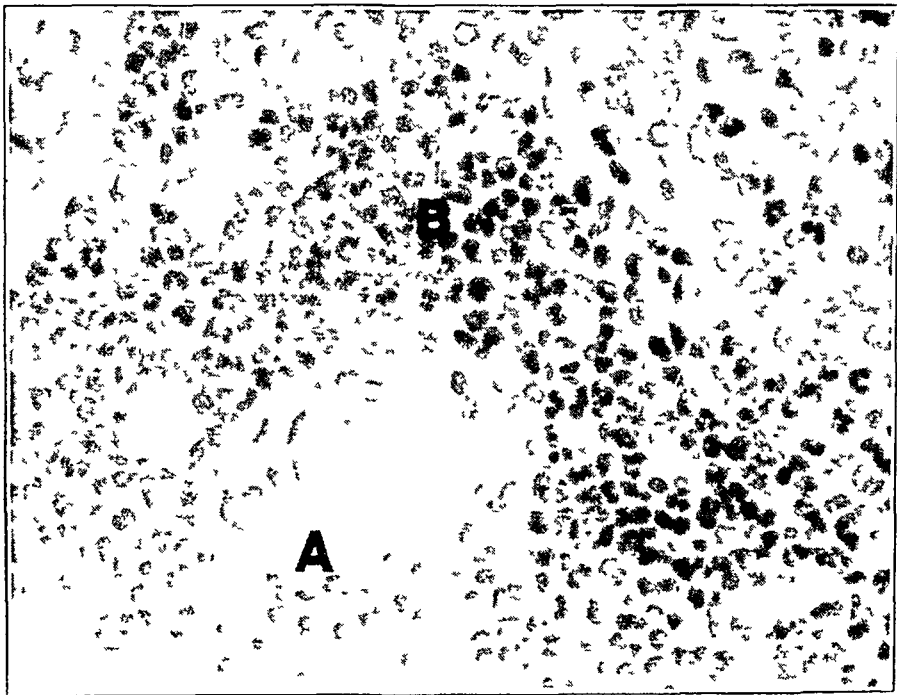


Fig 7 (case 4)—Hemorrhagic necrotic lesion. *A*, blood vessel, *B*, perivascular infiltration with eosinophils.

disappeared from the peritoneal fluid as well as from the blood. The asthma also subsided, to return one year later after the abdominal fistula resulting from the infarction had closed.

The distinguishing features in cases 7 and 8, in addition to the asthma and the pulmonary and myocardial involvement, were the development of irreversible electrocardiographic changes and adhesive pericarditis. In the course of hospitalization the patients in both of these



Fig 8 (case 7)—Specimen of skin taken for biopsy. *A*, nerve surrounded by edematous tissue and showing infiltration with eosinophils, *B*, blood vessel surrounded by eosinophils.

cases presented the symptoms of “constrictive pericarditis.” With the appearance of eosinophilic exudates in the pleura and peritoneum the syndrome of polyserositis came to the fore. Other important manifestations present were polyneuritis, which persisted for a number of weeks, and various cutaneous lesions. In case 7 the latter were marked by urticaria and by purpura of both upper and lower extremities. On biopsy material from the purpuric spots showed perivascular eosinophilic infiltrations. In case 8, in addition to urticaria and purpura, there

developed angioneurotic edema of the face and larynx and subcutaneous nodules over the forearms, which disappeared completely after two weeks. A biopsy of material from one of these nodules disclosed an inflammatory reaction characterized by perivascular eosinophilic infiltrations similar to those in cases 4 and 7 in some of the sections and lesions typical of periarteritis nodosa in others (figs 7 through 10)



Fig 9 (case 8) —Subcutaneous nodule *A*, blood vessel, *B*, perivascular infiltration with eosinophils

LABORATORY DATA

Examination of the sputum of each of the asthmatic patients disclosed eosinophilia. The bacterial flora was variable and nonspecific. It included pneumococci, *Streptococcus haemolyticus*, *Streptococcus viridans*, *Staphylococcus aureus*, *Staphylococcus albus*, *Micrococcus catarrhalis*, Vincent's spirillae and other organisms.

Bone marrow obtained by punctures of the sternum in cases 5 and 7 showed a marked increase in eosinophils. Blood cultures were sterile in every case in which they were made (cases 4, 5, 6, 7 and 8).

The blood counts were characterized by the number of leukocytes, ranging from a minimum of 7,000 to a maximum of 40,000, and by the percentage of eosinophils, ranging from 7 to 84 (table). The pleural and peritoneal fluids were sterile on culture, the specific gravity was 1.015, and the eosinophil content varied from 85 to 100 per cent.

The bacteriologic studies of washings from the sinuses disclosed the following organisms: *Staphylococcus aureus haemolyticus*, in case 1,



Fig. 10 (case 8)—Subcutaneous nodule: *A*, periarthritis nodosa completely involving a vessel wall; *B*, eosinophils.

Staph. aureus, *Staph. albus* and *Str. viridans*, in case 5, and *Staph. aureus* and *Staph. citreus*, in case 6. The results of cultures in the rest of the cases were not available (table).

COMMENT

Pulmonary Lesions—An analysis of the character of the pulmonary lesions displayed by these patients disclosed that they were insidious in onset, migratory in nature, miliary and interstitial in distribution and occasionally exudative (cases 1 and 8), simulating tuberculosis. They were accompanied by temperatures ranging between 100 and

102 F, cough, asthma and eosinophils in the sputum. Often the pulmonary lesions were not detected by physical examination, and their presence was discovered by roentgen ray examination only. Cases in which there were fugitive pulmonary signs without asthma have been previously recorded by Löffler,⁷ Engel,⁸ Rohner,⁹ Wernli-Haessig,¹⁰ Gsell¹¹ and others. Similar pulmonary manifestations were reported by Cole and Korns¹² under the name of "visceral manifestations of angio-neurotic edema" and by Vaughan and Hawke¹³ under the title of "angio-neurotic edema with some unusual manifestations." The latter authors, as well as Cole and Korns, concluded that in the cases they reported the pulmonary lesions were expressions of a more or less disseminated "angio-neurotic" edema due to foods. The absence of asthma in the majority of the cases reported indicates that inflammatory reactions in the lungs due to allergy may occur independently of bronchial asthma, a fact which has been proved experimentally by Fried¹⁴ and by others.

The cases here reported differed from those of Löffler in the more prolonged duration of the infiltrations and the presence of large effusions which had to be aspirated. While the exact nature of the pulmonary lesions in these cases cannot be fully established, the probability is that they represent hyperergic forms of response in which the interalveolar capillaries, the larger vessels and the associated mesenchymal structures participated. The resultant interstitial edema and cellular infiltration could therefore account for the peculiar appearance in roentgenograms.

In support of this view the following arguments may be offered:

- 1 The shadows in the roentgenograms lacked the homogeneous character of those produced in cases of pneumonia.
- 2 Their miliary and interstitial appearance suggested a hematogenous rather than an alveolar distribution.
- 3 Their fluctuation in extent and duration with the appearance and termination of the asthmatic paroxysm and the eosinophilia of the sputum and blood, present in 6 out of the 8 cases, suggested not only a reversibility common to allergic vascular reactions, such as

7 Löffler, W. (a) Zur Differential-Diagnose der Lungeninfiltrationen, über fluchtige Succedan-Infiltrate mit Eosinophilie, Beitr z Klin d Tuberk **79** 368, 1932, (b) Die fluchtige Lunginfiltrate mit Eosinophilie, Schweiz med Wchnschr **66** 1069, 1936.

8 Engel, D. Zur Frage des anaphylaktischen Frühjahrsödems der Lunge, Beitr z Klin d Tuberk **89** 323, 1937.

9 Rohner, H., in discussion on Löffler ^{7b}

10 Wernli-Haessig, A., in discussion on Löffler ^{7b}

11 Gsell, O., in discussion on Löffler ^{7b}

12 Cole, J., and Korns, H. M. Visceral Manifestations of Angio-Neurotic Edema, J Allergy **5** 347, 1933.

13 Vaughan, W. T., and Hawke, H. K. Angio-Neurotic Edema with Some Unusual Manifestations, J Allergy **2** 125, 1931.

14 Fried, B. M. Allergic Inflammation of Lungs, Arch Path **18** 865 (Dec) 1934.

urticaria, but also the participation of a common allergic excitant. Moreover, as noted previously, the development of hyperergic vascular lesions in the skin concurrently with those in the lungs, consisting of hemorrhagic necrosis in case 4 and purpura, urticaria and angioneurotic edema in cases 5, 6, 7 and 8, as well as periarteritis nodosa in case 8, gives additional support to the concept that the pulmonary reaction might be of a similar character. At autopsy, sections of the lungs of the patient in case 8, aged 38, disclosed thickening of the small vessels. Whether this represented the remains of allergic inflammatory reaction which did not progress to periarteritis nodosa, such as was seen in the vessels of the heart and liver in this case, is a matter for conjecture. Thickening of the pulmonary vessels in cases of long-standing asthma in which there was no manifest hyperergic vascular disease has been previously reported by Kountz and Alexander¹⁵. In a patient aged 11 whose case was recently described by Danziger,¹⁶ with a clinical picture identical in every respect with that in case 8 in this series, eosinophilic arteritis of the pulmonary vessels and infiltration of the interalveolar septums with eosinophils, lymphocytes and polymorphonuclear cells, as well as fibrosis, were found post mortem. The rest of the organs showed widespread periarteritis nodosa. It is evident, therefore, that changes in the vascular structures of the lungs or other organs in persons with asthma do not vary with the age of the patient but are related to the tempo of the allergic process. In Danziger's patient a subcutaneous injection of a minute quantity of vaccine prepared from sinus washings containing *Staph aureus* precipitated acute signs of infiltration in the lungs within twenty-four hours, as well as generalized purpura. In case 6 of this series 0.02 cc. of a 1:100,000 solution of a vaccine consisting of a mixture of *Staph aureus* A, *M catarrhalis* and *Streptococcus nonhaemolyticus* induced severe asthma and a generalized shock each time such a dose was injected. Such results signify not only that bacterial allergy exists but also that the blood vessels are the major shock tissue.

These observations suggest that the pathogenetic factors underlying the bronchial asthma in the cases studied consist of allergic reactions in the blood vessels as the basic shock tissue. It may be conceived that in cases of simple uncomplicated asthma such responses may be relatively mild and limited to the bronchi, under which circumstances the roentgen ray examination will show nothing abnormal. In cases in which the allergic process is intensified in degree as well as in extent, as in the cases under discussion, hyperergic reactions may ensue and embrace

15 Kountz, W. B., and Alexander, H. L. Death from Bronchial Asthma, *Arch. Path.* 5:1003 (June) 1928.

16 Danziger, J. Personal communication to the author. This case is being reported from Dr. Schick's service.

the vessels not only of the bronchi but also of the pulmonary parenchyma. Sensitization of these vessels results in increased permeability and edema. The elaboration of histamine-like substances involved in the allergic reaction, according to current teaching, plus the inflammatory eosinophilic exudate which infiltrates the musculature of the bronchi, probably accounts for the so-called muscle spasm. Histamine is known to produce spasm of smooth muscle experimentally. In cases of bronchial asthma of long duration the additional labor imposed on the bronchial musculature in expelling the air and the increased amount of viscid secretions from the inflamed bronchi may be regarded as being responsible for the muscular hypertrophy described by Huber and Koessler.¹⁷

Cardiac Manifestations—The participation of the heart was recognized by changes registered in the electrocardiograms. They were in the nature of abnormalities in the deflections and amplitudes of the P waves, T waves and QRS complexes, which were noted in 6 patients (cases 3, 4, 5, 6, 7 and 8). The alterations were accompanied by enlargement of the right and left ventricles in 2 patients (cases 5 and 8), of the right ventricle alone in 2 patients (cases 6 and 7) and of the left ventricle alone in 1 patient (case 4). It is significant that the electrocardiographic aberrations disappeared with the recession of the asthmatic paroxysms (figs 1, 2 and 3), the associated acute pulmonary infiltrations and the serous effusions. That these abnormal electrocardiographic changes were not dependent on the pleural effusions was evidenced by their appearance in the absence of or prior to the development of fluid (cases 3, 5 and 6). Their independence of the administration of epinephrine was likewise exemplified in case 5 by their reversion to the normal state with the termination of a major asthmatic paroxysm in spite of the continuous subsequent use of this drug for persistent wheezing. Moreover, in the average patient with asthma repeated administration of therapeutic doses of epinephrine for prolonged periods does not produce such electrocardiographic changes. That the deviations were not the result of respiratory anoxemia was noted by their persistence during intervals when the patient was free of asthma (cases 4, 5, 6, 7 and 8). During such periods symptoms in other shock tissues, such as skin (case 4), pericardium (case 5) and peritoneum (cases 6, 7 and 8), developed. The allergic character of these manifestations was suggested by the finding of perivascular eosinophilic infiltrations in biopsies of the skin in cases 4, 7 and 8 and the occurrence of a high percentage of eosinophils in the exudates of the various serous membranes involved. Inasmuch as the presence of eosinophils implied increased permeability of the capillaries which permitted their migration from the blood stream, it signified

17 Huber, H. L., and Koessler, K. K. The Pathology of Bronchial Asthma, Arch Int Med 30:680 (Dec) 1922.

the active participation of these vessels in the allergic response. This led to the inference that the coincidental electrocardiographic deviations were probably likewise brought about by similar reactions in the coronary vessels. Their reversibility or irreversibility was regarded as dependent on the individual degree of hypersensitiveness, the extent and duration of the vascular reaction and the injury to the myocardium sustained from the resulting ischemia. Proof of this was adduced in case 8 of this series, as well as in Danziger's case previously referred to, in both of which autopsies were done. Postmortem examination of the hearts in these cases showed varying degrees of hyperergic vascular disease involving the pericardium and the coronary vessels, progressing to the stage of periarthritis nodosa. The recently published cases by Clark and Kaplan¹⁸ of "serum carditis" in which autopsies were performed four and nineteen days, respectively, after serum sickness help to elucidate the concept that various degrees of allergic reactions may occur in the coronary vessels as a result of sensitization. Microscopic studies of the hearts in these cases disclosed "necrotizing arteritis and periarthritis of the small coronary arteries," in addition to histologic changes in the mural and valvular endocardium, as well as in the aorta and the pulmonary vessels. Inasmuch as the lesions resembled those found in cases of protracted anaphylaxis induced in animals by administration of foreign serum, the authors inferred that the alterations in the hearts of their patients were probably of a hyperergic nature and were related to the foreign serum administered.

Recent experimental work by Wilcox and Andrus¹⁹ adds further support to the foregoing clinical observations. These investigators were able to demonstrate, by using direct leads from the isolated perfused hearts of guinea pigs sensitized to horse serum, various electrocardiographic abnormalities usually associated with mechanical constriction of the coronary arteries on exposure to small amounts of homologous antigen. The deviations consisted of acceleration of the heart rate and alteration in the amplitude of contraction. The PR interval was prolonged, and there were changes in the form of the QRS and T complexes, as well as ectopic rhythms. They were also able to show that these changes were due to actual alterations in caliber of the coronary vascular system and not to an increase in heart rate or muscle tonus.

Serous Membranes—Coincidentally with the previously noted pulmonary and cardiac changes, symptoms pointing to the participation of the serous membranes, which according to Eppinger²⁰ implies capil-

18 Clark, E, and Kaplan, B. I. Endocardial, Arterial and Other Mesenchymal Alterations Associated with Serum Diseases in Man, *Arch Path* **24** 458 (Oct) 1937

19 Wilcox, H. B., and Andrus, E. C. Anaphylaxis in the Isolated Heart, *J Exper Med* **67** 169, 1938

20 Eppinger, H. *Die seröse Entzündung*, Berlin, Julius Springer, 1935

lary disease, presented themselves as follows In cases 1, 2 and 4 the pleura alone was involved, in case 5 the pleura and pericardium, in case 6 the pleura and peritoneum and in cases 7 and 8 the pleura, pericardium and peritoneum

The simultaneous involvement of the pleura and the pericardium in case 5 was followed by a so-called superior mediastinal syndrome This was characterized by high venous pressure, distention of veins in the neck, mediastinal pleuritis, pericarditis, gallop rhythm and electrocardiographic changes All of these signs subsided after three weeks During this episode, the dominant symptom asthma disappeared, only to return in full force after the cardiac manifestation had terminated

The reverse was true in cases 7 and 8 In both of these cases the patients ran the gamut of allergic responses during their stay in the hospital In case 8 the first stage was characterized by hypereirgic phenomena in the lungs, pleura, joints, skin and superficial vessels These were expressed clinically as bronchial asthma with pulmonary infiltrations, pleural effusions, polyarthritis, polyneuritis, urticaria, angioneurotic edema and periarteritis nodosa of superficial vessels The patient improved for a short while, during which time the periarteritic nodules disappeared This marked the reversible phase of his illness A second period, which may be designated as the irreversible stage, ensued, dominated by the clinical picture of chronic or fixed constrictive pericarditis This was characterized by progressive cardiac failure, permanent electrocardiographic changes indicating severe myocardial damage, pericarditis, mediastinitis, ascites and progressive enlargement and tenderness of the liver, which was diagnosed *intra vitam* and was proved at autopsy to be due to amyloidosis In the light of the generalized allergic reactions in this patient, the intercurrent amyloidosis may be explained as a phenomenon of hypersensitiveness mediated by the same allergenic stimulation as that responsible for the entire clinical picture That protein sensitization may be the cause of amyloidosis has been proved by Kuczynski²¹ and confirmed by Smetana,²² Jaffé,²³ Domagk,²⁴ Letterer²⁵ and Grayzel, Jacoby, Warshall, Bogin and

21 Kuczynski, M H Edwin Goldmanns Untersuchungen über cellulare Vorgänge im Gefolge des Verdauungsprozesses, *Virchows Arch f path Anat* **239** 185, 1922

22 Smetana, H Experimental Study of Amyloid Formation, *Bull Johns Hopkins Hosp* **37** 383, 1925

23 Jaffé, R H Amyloidosis Produced by Injection of Proteins, *Arch Path* **1** 25 (Jan) 1926

24 Domagk, G Untersuchungen über die Bedeutung des retikuloendothelialen Systems für die Vernichtung von Infektionserregern und für die Entstehung des Amyloids, *Virchows Arch f path Anat* **253** 594, 1924

25 Letterer, E Studien über Art und Entstehung des Amyloids, *Beitr z path Anat u z allg Path* **75** 486, 1926

Bolker,²⁶ who employed bacterial proteins as well as gelatin, egg albumin, nuclein and peptone in the experimental production of amyloidosis in various mesenchymal tissues. With the advancing anasarca resulting from cardiac failure, on the one hand, superimposed on the existing hypoproteinemia and allergic polyserositis, on the other, a third and final phase, the stage of anergy, ensued. In this phase, while the patient was bereft of all mechanisms of defense, the onset of acute pneumonia brought the clinical course to a swift and fatal termination.

Although no evidence of periarteritis nodosa, such as was obtained in case 8, could be adduced during life in case 7, the patient in this case presented a clinical picture identical with the one just described. It included chronic sinusitis, asthma with marked eosinophilia, adhesive pericarditis, eosinophilic peritonitis, enlargement of the liver, purpura, urticaria, angioneurotic edema, polyarthritides, polyneuritis and, finally, cardiac failure associated with signs of constrictive pericarditis. Biopsy (fig. 8) of material from a purpuric lesion of the skin of this patient showed subepidermal edema and perivascular and perineural infiltration with eosinophilic leukocytes but no distinct involvement of the vessel walls themselves. In this case, as well as in case 8, the polyneuritis could in all probability be explained on the basis of such a perineural edema and infiltration, while the fugitive polyarthritides was probably due to similar reactions in periarticular vessels. The perivascular eosinophilic infiltrations were identical with those observed in some of the areas of the sections of the periarteritic nodule removed for biopsy in case 8 (fig. 9). They also resembled in histologic appearance the urticarial wheals experimentally produced by injection of an allergen, such as ragweed or tobacco, into the skin of persons sensitive to these substances. It may be argued, therefore, that they represented reactions of hypersensitiveness to allergenic stimulation and, together with the rest of the symptoms, were expressions of a generalized mesenchymal response in which sensitized blood vessels and capillaries played the cardinal role. On the basis of these observations the following hypothesis seems reasonable.

Just as asthma may be regarded as a manifestation of sensitization of the blood vessels and of other mesenchymal structures in the lung, so might the symptom complex of mediastinopericarditis (case 5) or constrictive pericarditis, noted in the early stages in cases 7 and 8, represent the sequelae of allergic responses in the vessels of the serous membranes of the pericardium, mediastinal pleura and myocardium. Since the progressive involvement of the visceral pleura and peritoneum in the last 2 cases mentioned led to the clinical picture of polyserositis, it follows that this syndrome, being merely the result of extension of the underlying

26 Grayzel, H. G., Jacobi, M., Warshall, H. L., Bogin, M., and Bolker, H. Amyloidosis. Experimental Studies, *Arch. Path.* 17:50 (Jan.) 1934.

allergic process to other serous membranes in the same persons, must also be regarded as an expression of sensitization. It is therefore suggested that polyserositis occurring in persons without a frank allergic background or the tendency to eosinophilia may likewise represent hypersensitiveness of serous membranes in nonatopic persons to some fundamental infection. Thus, for example, the polyserositis associated with tuberculosis may be an expression of allergic reaction to the tubercle bacillus. To this category may also belong the 2 cases reported by Löffler²⁷ of so-called Pick's syndrome, of unknown cause, in which during life in spite of a negative history of allergy the patients had eosinophilia, with an eosinophil count of 70 per cent and a total leukocyte count of 18,000. Autopsy disclosed obstruction to the inflow tract in the right ventricle caused by fibrinoplastic endocarditis of undetermined origin.

The presence of eosinophilia in Löffler's patients aids in their identification as members of the allergic group, even though the picture of Pick's syndrome which they presented was the result of a mechanical obstruction due to the lesion in the endocardium rather than to generalized active participation of the serous membranes. Absence of eosinophilia, however, need not exclude a given case from being placed under the rubric of allergy provided the pathogenesis of the presenting symptoms is similar to that which obtained in the cases described in this report.

The contrast between a clinical course which is subject to allergenic stimulation and one which follows direct bacterial invasion is well illustrated by case 6. In this case an inflammatory reaction in a mesenteric vessel, presumably on a hyperergic basis, brought about thrombosis and infarction of the intestinal wall followed by perforation. The consequent direct bacterial invasion of the peritoneum caused suppurative peritonitis. A relative state of anergy supervened, and the patient's condition became alarming. The eosinophils disappeared completely from the peritoneal fluid, as well as from the peripheral circulation. Culture of the ascitic fluid showed *Bacillus coli*, enterococci and *Bacillus proteus*. The peritoneal suppuration became localized, and an abscess formed, with a fistulous opening, through which subsequently drained malodorous pus containing various unidentified gram-positive and gram-negative cocci and bacilli, *B. coli*, *Salmonella paratyphi* and *Salmonella schottmulleri*. Blood transfusions brought about improvement in the patient's condition, and eosinophils began gradually to reappear. Throughout this stormy period the bronchial asthma was in abeyance. The abscess gradually healed, and the patient was discharged. At the time of his departure from the hospital (November

²⁷ Löffler, W. Endocarditis parietalis fibrinoplastica mit Bluteosinophilie, Schweiz. med. Wchnschr. 66: 817, 1936.

1935) he had no asthma and the blood count showed 9,100 white cells, with 64 per cent polymorphonuclear leukocytes and 24 per cent lymphocytes, but no eosinophils. One year later, after the abdominal fistula had closed, the asthma returned. The patient's subsequent departure from the United States precluded further observations. The findings in other cases in this series, however, such as in case 5, in which eosinophils dropped from a maximum of 55 per cent during the acute paroxysms to 15 per cent in intervals free of asthma, indicate that while these cells persist between acute attacks they become greatly reduced.

Eosinophilia—Variations in the values for eosinophils in the blood of allergic persons suffering from similar or different forms of hypersensitiveness are common. In many instances of asthma and other types of allergic disease, the eosinophil content of the peripheral circulation may not exceed the normal limits of 2 to 4 per cent. This does not exclude, however, the possibility of a concentration of eosinophils within the reacting shock organ. The marked eosinophilic infiltration of the walls of the bronchi repeatedly demonstrable post mortem in patients with asthma who had normal blood counts during life is evidence of this fact. In a review of the findings of a number of investigators, Hunt²⁸ recorded that the percentage of eosinophils in the blood of the average patient with asthma rarely rises above 5 to 9, with the total leukocyte count within normal limits. The remarkable rise in the total number of white blood cells to 40,000 and in the percentage of eosinophils to 50 in the peripheral circulation in the cases here described, paralleled by a concomitant increase in these cells in the bone marrow, as shown by the sternal punctures in cases 5 and 7, indicated that the hemopoietic tissues participated in the generalized allergic response. The bone marrow may therefore be regarded as a shock organ which may react under allergenic stimulation by multiplication of its cellular elements or by suppression, as exemplified by the picture of agranulocytosis in persons sensitive to various drugs and chemical substances. Marked eosinophilia accompanying bronchial asthma may consequently serve not only as a quantitative index of the degree of the allergic response but also as a diagnostic point for differentiation between asthma associated with a generalized mesodermal reaction in which the vascular system plays a prominent role and asthma confined to the bronchial tissues alone.

Etiologic Agents and Course of Disease—A review of the histories and the clinical findings in these cases indicates that the character, extent and duration of the course of the disease depended on the degree of susceptibility of the patient and on the nature and the number of sensitizing agents, as well as on the number and character of the shock

²⁸ Hunt, H. B. Some Observations on the Blood Eosinophile Count in Asthmatics, *J. Allergy* **10** 146, 1939

organs involved Although remissions in the attacks without the influence of any specific therapy were observed in cases 3, 4 and 5, the duration of such improvement was short and unpredictable Success in therapy was proportional to the availability of means for controlling the various factors enumerated and eliminating the major offending allergens This was feasible in case 1 The close correlation in the seasonal appearance of the pulmonary manifestations and the pollination periods of timothy and ragweed led to the conclusions, verified by positive cutaneous reactions, that these pollens were of major etiologic importance in producing the symptoms in this case, while the sinus infection was of secondary concern Washing the sinuses till the returned fluid was clear and perennial immunization with the incriminating pollens, together with elimination of foods to which the patient was found to be sensitive, have resulted in freedom from attacks for the past three years When, however, bacterial allergy dominated the clinical picture, as in cases 2 and 6, immunization with pollen to which the patients were found sensitive proved to be ineffective in preventing attacks As noted previously, an attempt by his physician to immunize 1 patient (case 6) with an autogenous vaccine failed because he was so sensitive to the bacteria contained therein that each injection produced a violent systemic reaction terminating in asthma and shock As a consequence the patient refused further treatment Subsequent operations on his sinuses proved equally futile in preventing recurrences of asthmatic attacks In case 5 injections of a vaccine containing *Staph aureus* A, isolated from the sinuses, also were found to be ineffective The lack of success in this case may have been due to the fact that the recovered micro-organisms were merely secondary surface bacteria and not the primary exciting agent The latter, according to Grove and Cook,²⁹ are most apt to be cultivated from mucous membranes removed from diseased sinuses at operation

Since asthmatic attacks in these and other cases are frequently ushered in by infections of the respiratory tract, in which viruses may play an important role, sensitization not only to the latter but also to the secondary invaders may come into question Moreover, under such circumstances, in addition to sensitivity to bacterial proteins, sensitization to their toxins may also supervene Thus in bacterial allergy one is confronted with the synergistic effects brought about by viruses, bacteria and toxins How to deal with these various factors, at the present stage of knowledge, is a complex problem This accounts for the unsuccessful results with vaccine therapy in many

29 Grove, R C, and Cook, R A Etiology and Nature of Chronic Hyperplastic Sinusitis, *Arch Otolaryng* 18 622 (Nov) 1933

cases of the more serious forms of the disease. Whether under such circumstances the proper procedure consists in radical surgical treatment of the sinuses, as advocated by Cook, with the idea of eliminating an important focus of infection which may sensitize other organs is a question which deserves consideration. While this approach has been reported to be successful in the average case of uncomplicated asthma, the technical operative difficulties involved in some cases, coupled with the uncertainty that in the cases of the more sensitive patients with progressive disease, such as those previously described, the sinuses may not be the only sources of allergenic stimulation, militate against the unqualified success of surgical intervention. Thus, as indicated operations on the sinuses in cases 5, 6, 7 and 8 did not prevent recurrences of asthma. As a matter of fact, in the last 2 cases the patients were so ill on admission to the hospital that only symptomatic therapy could be instituted. These unfavorable results may be explained on the ground that bacterial allergy, in contrast to simple controllable nonbacterial protein hypersensitiveness, may be reactivated not only by contact with homologous bacterial agents responsible for the initial sensitizing effect, but also, in the light of Shwartzman's³⁰ observations, by heterologous bacteria and then toxins, as well as by antigen-antibody complexes of nonbacterial origin. This was exemplified in case 4 of this series, recently discussed in a report by Harkavy and Romanoff.³¹ Such nonspecific effects, therefore, explain why every fresh "cold" or infection of the respiratory tract in patients with chronic sinus disease, or even in those whose sinuses have been previously operated on, may be followed not only by recrudescence of asthma but by symptoms in other shock tissues present in the patient which are subject to the same allergenic excitants, such as the heart, the pericardium and the pleura. These reactions may occur simultaneously or alternately with the asthmatic paroxysm, as illustrated in cases 5, 6, 7 and 8. In view therefore of the many complicating factors involved in dealing with manifestations of bacterial hypersensitiveness, therapy must be individualized. In the moderately sick patient treatment of diseased sinuses, control of inhalant and food allergens and, in special instances, autogenous vaccine therapy may be followed by favorable results. When dealing with cases of severe bacterial asthma, however, such as the cases herewith presented, a more conservative approach, such as change of environment to a warm, dry climate, offers the better outlook. This was found to be the solution in case 2 of this group, in which the patient has been free of asthmatic attacks and

30 Shwartzman, G. *Phenomenon of Local Tissue Reactivity*, New York, Paul B. Hoeber, Inc., 1937.

31 Harkavy, J., and Romanoff, A. Local Hemorrhagic-Necrotic Skin Reactions in Man (Shwartzman Phenomenon), *J. Allergy* **10** 566, 1939.

pulmonary lesions during the past three years while living in Arizona. This result may be contrasted with that in case 6, in which the patient who also was well while in Arizona became seriously ill on returning to New York, in spite of extensive operations on the sinuses and symptomatic therapy.

SUMMARY

Eight cases, in 7 of which the patients suffered from typical bronchial asthma and in 1 of which the patient had bronchospasm and cough, are reported. The exciting factors in 2 of these cases were identified as synergistic sensitization to pollen, foods and bacterial products, while in the remaining 6, bacterial allergy resulting from chronic sinus infections played the important role.

The major attacks of asthma were associated with migratory inflammatory interstitial lesions in the lungs, with eosinophils in the sputum, and also with reactions in the serous membranes characterized by pleural effusions in 6 cases and by peritoneal exudates and pericardial involvement in 3 cases.

The aspirated fluids were sterile, and the eosinophil content ranged up to 100 per cent.

The pericardial reactions took the form of acute pericarditis, which reverted to normal within three weeks in 1 case and progressed in 2 others to a chronic adhesive stage.

Coincidentally with the asthmatic attacks and with the pleuropulmonary involvements, there appeared electrocardiographic abnormalities in the deflections and amplitudes of the T waves and the QRS complexes. These returned to normal with the termination of the asthmatic seizures in 4 cases and remained permanent in 2 cases, in the latter cases the patients ultimately died.

Other important features were an increase in eosinophils in the blood in all cases, at times to 84 per cent, fugitive polyarthritides and polyneuritis in 3 cases, hemorrhagic necrosis in the thigh in 1 case, and urticaria, angioneurotic edema and purpura in 2 cases, in 1 of which subcutaneous nodules also developed.

Biopsies of material from the cutaneous lesions and from a subcutaneous nodule disclosed perivascular eosinophilic infiltrations. In addition, the subcutaneous nodule also showed areas of periarteritis nodosa.

Bone marrow obtained by sternal puncture gave evidence of marked increase in the eosinophilic granulocytes.

The occurrence of eosinophils in the sputum, in the serous exudates and in the perivascular infiltrations in the skin, associated with periarteritis nodosa in 1 case, implies active involvement with increased permeability of vessels of the lungs, serous membranes and cutaneous tissues. Thus it would seem reasonable to assume that the recurrent

interstitial pulmonary infiltrations revealed on roentgen ray examination, accompanied by the presence of eosinophils in the sputum, the eosinophilic exudates in the pleura and the electrocardiographic changes, were probably also due to vascular reactions in the respective tissues similar to those revealed by biopsies of the skin.

In view of the fact that the asthmatic paroxysms ran a course parallel with that of the pulmonary lesions, they may be considered as symptomatic expressions of the underlying reactions in the vessels of the lungs and bronchi. Since these asthmatic seizures appeared simultaneously with manifestations of altered vascular responses in other shock organs consequent on the same allegenic stimulation, they must be regarded as but one aspect of a more diffuse vascular and mesodermal reaction.

The fact that involvement of the vessels in the various serous membranes and the heart in this generalized response resulted in 1 case in the clinical picture of mediastinopericarditis, which resolved completely, and in 2 cases in constrictive pericarditis and subsequently in polyserositis suggests that these syndromes were the sequelae of hyperergic vascular reactions in the serous membranes and the myocardium.

The reversible electrocardiographic changes appearing concurrently with the asthma and the pleuropulmonary lesions in 4 of the cases were probably influenced by the same allegenic mechanism. In 1 of the 2 cases in which the electrocardiographic changes were irreversible, thickening of small arteries, arteritis and perivascular fibrosis were found in the myocardium at autopsy.

The presence of eosinophils in the perivascular infiltrations observed in biopsies of the skin in cases 4 and 7, as well as in certain areas of the subcutaneous nodule examined in case 8, which likewise contained blood vessels in various stages of involvement progressing to periaarteritis nodosa, testifies to the allegenic nature of these vascular reactions and strongly supports the view that periaarteritis nodosa represents a hyperergic vascular response.

Demonstration of an increase in the percentage of eosinophils, as well as in the total number of white blood cells, in the bone marrow indicates that the marrow participated as a shock organ.

CONCLUSION

From the observations recorded here it may be inferred that the various manifestations under discussion represent responses in different organs in which primary sensitization of blood vessels plays the determining role. It is evident that in some patients (case 4) the resultant reactions of the pulmonary tissue may be expressed clinically as bronchitis and cough and in others by paroxysms of asthma. Either

the bronchitis or the asthma may disappear completely under causal therapy, without leaving any visible pathologic changes. This may be regarded as a reversible reaction characteristic of most of the simple and readily controlled manifestations of hypersensitiveness. In the more severe types of polyvalent sensitivity, especially those in which bacteria assume a dominant, as well as synergistic, role in conjunction with other excitants, allergic inflammation in the various structures of the lung may become more extensive and profound insofar as it is augmented by the destructive effect of bacterial toxins (case 4).

Not only the bronchi and other portions of the pulmonary tree, but the myocardium, the serous membranes, the joints, the skin and the nervous and hemopoietic systems may likewise be involved in the more generalized vascular reactions. Under such circumstances there arise distinct syndromes which also may be reversible or irreversible, the allergic nature of which may be recognized by the asthma and the eosinophilia. These syndromes are determined by the number, character and variations in the combinations of the shock tissues affected. Thus, there may be a pulmonary-myocardial, a pleuropulmonary-myocardial or a pleuropulmonary-myopericardial response which will result in the picture of constrictive pericarditis. Finally, with the extension of reactions to all of the serous membranes, the characteristic symptoms of polyserositis become apparent. In the presence of these fundamentally allergic responses, disturbances in the dynamic aspects of the circulation are inevitable. Although these symptom complexes seem to be clinical entities, it should be emphasized that they are not of an essentially independent origin but are merely varying expressions of a state of hypersensitiveness. The identity in their basic mechanism, in spite of variations in the clinical pictures, supported by the pathologic lesions in the biopsy sections, especially in case 8, in which were seen gradations from simple perivascular eosinophilic infiltration (cases 4 and 7) to the full picture of periarteritis nodosa, suggests that 7 of the 8 cases reported here illustrate varying degrees of hyperergic vascular responses, the ultimate stage of which is represented in the periarteritis nodosa observed in case 8. They may be regarded as *formes frustes* or potential types of this disease.

CHRONIC HEMOLYTIC ANEMIA WITH PAROXYSMAL NOCTURNAL HEMOGLOBINEMIA

REPORT OF A CASE WITH ONLY OCCASIONAL HEMOGLOBINURIA
AND WITH COMPLETE AUTOPSY

GEORGE C HAM, MD*

AND

HAROLD M HORACK, MD

Assistant Instructor in Pathology, University of Pennsylvania School of Medicine
PHILADELPHIA

A clinical syndrome characterized by chronic hemolytic anemia associated with paroxysmal nocturnal hemoglobinuria was independently described by Marchiafava¹ in 1928 and Micheli² in 1931. Since then several investigators³ have reported on the clinical manifestations of the disease, but its mechanism remained unknown until 1937, when T H Ham⁴ demonstrated the nature of the factors responsible for the production of the hemolysis.

In a recent article in this journal T H Ham⁵ made the first comprehensive report on these factors. He demonstrated that the fundamental abnormality in this disease resides in the red blood cells, and not in the serum. He showed that the red blood cells of patients with the disease were abnormally sensitive to slight changes in p_H . Lowering the p_H , even within the physiologic range, always caused increased hemolysis, and raising the p_H reduced or eliminated the hemolysis.

Ham also demonstrated the presence of a thermolabile factor essential to this hemolytic mechanism which is present in all human serums but has no effect on normal erythrocytes.

From the Medical Clinic of the Hospital of the University of Pennsylvania.

* Edward Bok Fellow and Resident in Medicine, Hospital of the University of Pennsylvania.

1 Marchiafava, E. Anemia emolitica con emosiderinuria perpetua, *Polichinico (sez med)* **35** 105, 1928, **38** 105, 1931.

2 Micheli, F. Anemia (splenomegalia) emolitica con emoglobinuria-emosiderinuria tipo Marchiafava, *Haematologica (I Arch)* **12** 101, 1931.

3 (a) Witts, L J. Paroxysmal Haemoglobinurias, *Lancet* **2** 115, 1936.
(b) Hamburger, L P, and Bernstein, A. Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria, *Am J M Sc* **192** 301, 1936.

4 Ham, T H. Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria. A Study of the Mechanism of Hemolysis in Relation to Acid-Base Equilibrium, *New England J Med* **217** 915, 1937.

5 Ham, T H. Studies in Destruction of Red Blood Cells, *Arch Int Med* **64** 1271 (Dec) 1939.

He showed by *in vivo* studies that intravascular hemolysis occurs continuously in patients with this disease. The rate of hemolysis is increased during sleep, and hemoglobinuria appears when the level of free hemoglobin in the plasma exceeds the renal threshold. This threshold varies widely.

Administration of acid salts to these patients produced a significant increase in the acidity of the peripheral arterial blood and was associated with a transient increase in the degree of hemoglobinemia. Conversely, the administration of alkaline salts or the production of alkalosis by hyperventilation was associated with a transient decrease in hemoglobinemia.

The nocturnal increase in hemoglobinemia was shown to be associated with sleep and not with the patient's posture, with ingestion of food or with the time of day or night during which sleep occurred. It was felt probable that the increased intravascular hemolysis which occurs during sleep was related to an increase in the acidity of the blood, especially in areas of the body where circulation is relatively inactive during sleep, such as the spleen. Observations on the immunologic aspects of the disease have also been recently reported by the same author.⁶

The clinical picture presented by patients with this disease is one of chronic hemolytic anemia which is in most cases, but not always, associated with hemoglobinuria following sleep. Frequently there is a moderate degree of splenic enlargement, but this is not present in all cases. Moderate leukopenia and thrombocytopenia, which tend to return to normal levels if a therapeutic splenectomy is performed, have been observed in most patients. The urinary excretion of the products from the breakdown of hemoglobin is not quantitatively comparable to the amount of available free hemoglobin in the circulating blood plasma. The concentration of urobilinogen and porphyrins in the urine is normal or only moderately elevated. Impaired renal function is observed in some cases.⁵

The present article deals with a case in which the element of hemoglobinuria was inconspicuous and at times absent and in which application of the clinical and laboratory principles as outlined by previous investigators led to a definite diagnosis. A complete autopsy was performed.

REPORT OF CASE

History—A married white woman aged 46 was first admitted to the University Hospital in June 1935 complaining of weakness, fatigue and recurrent attacks of jaundice during the one and one-half years prior to admission. Her past medical

6 Ham, T. H., and Dingle, J. H. Studies on Destruction of Red Blood Cells. II. Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria, Certain Immunological Aspects of the Hemolytic Mechanism with Special Reference to Serum Complement, *J. Clin. Investigation* **18** 657, 1939.

history was essentially without significance. On physical examination the skin and mucous membranes were pale and slightly icteric. The spleen was palpable. Laboratory studies showed macrocytic anemia, with 2,800,00 red cells per cubic millimeter, a hemoglobin concentration of 67 per cent, a cell volume index of 1.05, a color index of 1.16, reticulocyte values of 9.5 and 11.5 per cent and leukocyte counts ranging from 3,400 to 4,900, with normal differential smears. The platelets numbered 230,000 per cubic millimeter. The red cells showed normal resistance to hemolysis by varying strengths of hypotonic solution of sodium chloride, those of the other members of her family were likewise normal in this respect. The coagulation time of the venous blood was ten minutes, and the bleeding time was two minutes. A van den Bergh test gave a delayed direct reaction and an indirect reaction of 1.8 units. Examinations of the urine, including tests for urobilin and bilirubin, repeatedly gave negative results. The diagnosis of atypical hemolytic anemia was made, and the patient was transferred to the surgical service for splenectomy. The spleen weighed 305 Gm. The surgical pathologic picture was not characteristic of any particular disease, and no definite histologic diagnosis was made. The patient made an uneventful recovery and after several transfusions was discharged.

The patient was in fair health for six months following operation, except for several episodes of jaundice. However, toward the end of that period she began to have attacks of pain in the right upper quadrant of the abdomen, which were associated with occasional bouts of vomiting and postprandial distress of increasing severity. Because of these symptoms she returned to the hospital in January 1936. Laboratory studies again showed moderate macrocytic anemia with reticulocytosis and an indirect van den Bergh reaction. The osmotic resistance of her erythrocytes was normal on several occasions. A cholecystogram showed a partially functioning gallbladder but no evidence of stones. Material obtained by duodenal drainage showed neither cholesterol nor calcium bilirubinate crystals. Because of her apparently poor response to splenectomy the possibility that she might have an accessory spleen was considered. Cholelithiasis was suspected because of its common association with chronic hemolytic anemia. An exploratory laparotomy was offered, but the patient refused surgical treatment and was discharged.

Her symptoms persisted, and in May 1936 she was again admitted to the hospital. She was pale and cachectic. She had a spiking temperature and an elevated pulse rate. There were bilateral hydrothorax and ascites. Hematologic studies gave essentially the same results as on the previous admissions. Extensive laboratory and roentgenologic investigations failed to reveal any specific cause for her symptoms. Under supportive medical management, including paracenteses and transfusions, her condition improved, and at the time of discharge she was afebrile and asymptomatic and had reached her normal weight and hemoglobin level.

The patient was not seen again for two years, and during that time she felt fairly well and was able to do her own housework. However, in August 1938 she returned to the hospital because of increasing dyspnea on exertion and failure of her blood count to respond to therapy. On this admission there was anemia, with about 3,000,000 red cells per cubic millimeter and a reticulocyte response of 7.5 per cent. Results of other studies of the blood and urine were the same as on previous admissions. The general physical examination showed nothing abnormal, and there was no evidence of reaccumulation of fluid in the serous cavities. She was given three blood transfusions and discharged.

Her last admission, on Oct. 15, 1939, was occasioned by the development of a new group of symptoms in addition to those which had previously necessitated

her hospitalization. She stated that approximately one year before admission she first noticed pain in her back. This pain gradually increased in severity. Several weeks before admission it became sharply localized in the upper lumbar region and was associated with pain in both legs. On admission she was unable to hold herself erect and walked about supporting her trunk by grasping the upper portions of the thighs with her extended forearms. Roentgenographic studies of her spine showed a spontaneous fracture of the twelfth thoracic vertebral body, which the roentgenologists felt was due to tuberculosis. The consultant in orthopedics concurred in the opinion that the patient had tuberculosis of the spine and suggested performing a Hibb fusion in an effort to stabilize the pathologic fracture.

Because the history and accumulated laboratory data were consistent with a chronic hemolytic anemia in which the results of fragility tests were repeatedly normal, it was felt by one of us (G. C. H.) that this patient's condition might represent paroxysmal nocturnal hemoglobinuria of the Marchiafava-Micheli type.

In a review of the hospital record of her past admissions no history of hemoglobinuria was found. Likewise, multiple urinalyses during these past admissions showed no trace of hemoglobin in the urine. However, on close questioning, the additional history was obtained that prior to the splenectomy the patient had noticed that her morning urine had frequently been very dark, but that during the four and one-half years since the operation she had passed dark urine only on three occasions. She had thought that the dark color was due to "blood" and stated that her physician examined her urine on those occasions but never found any red cells. She said that neither before nor after the splenectomy had she ever noticed any abnormalities in her urine, except in the first specimen in the morning. In the light of this additional history and the previous laboratory data, *in vivo* and *in vitro* studies were made which verified the diagnosis. These studies are described in the section on special diagnostic methods.

With the patient under general anesthesia a Hibb fusion of the lower thoracic and the upper lumbar portion of the spine was performed. Except for postanesthetic hemoglobinuria, which will be described later, the patient's postoperative course was uneventful until three weeks after the operation. At that time, as she was about to be allowed up, complete left hemiplegia developed. Her course thereafter was progressively downhill. Cystitis secondary to urinary retention and basal pneumonia developed, and the patient died on Jan. 23, 1940. Permission for necropsy was obtained.

Necropsy Examination—Gross Observations. Necropsy was performed six hours after death. The subject was poorly nourished, and the skin and mucous membranes were pale. Over the lower thoracic and upper lumbar portions of the spine there was an old surgical incision with a central area of nonunion, which contained yellowish gray seropurulent material. There was obvious atrophy of the left arm and leg. The serosal surfaces of the abdominal, pleural and pericardial cavities were covered with large, dense masses of old fibrous adhesions.

The heart weighed 280 Gm. There were loose fibrous adhesions which almost obliterated the pericardial cavity, no tubercles or granulation tissue was found. The myocardium was fatty. The valves were normal. There was slight atheromatous streaking of the aorta and the major vessels. The lungs weighed 240 Gm. each. Both pleural spaces were obliterated by dense fibrous adhesions. The lungs were intensely congested and moderately edematous. In the base of the lower lobe of the right lung there were a few small areas of deep reddish purple discoloration and increased resistance. There was no gross evidence of old or active pulmonary tuberculosis and there was no vascular thrombosis.

The liver weighed 2,500 Gm. There was dense fibrous perihepatitis. The liver was a dull, dark reddish brown and showed considerable variation in the distinctness of the lobular marking, as well as in the consistency of the tissue. A few of the large intrahepatic veins contained soft, friable thrombi, which were loosely adherent to the walls but did not occlude the lumens. The hepatic lymph nodes were enlarged, firm and loosely matted together, and their normal structure was replaced by a homogeneous, grayish yellow granular material. There were dense fibrous adhesions about an otherwise normal gallbladder. The pancreas, which weighed 125 Gm., was grossly normal. The spleen was absent. No splenuli were present. In the medulla of the left adrenal gland was a single delicately fibrous nodule. It was not encapsulated, measured 1.0 cm. in diameter and was yellowish gray. The right adrenal gland was normal.

The left kidney weighed 200 Gm., and the right one 180 Gm. They were large, and their capsules stripped with increased resistance, exposing dark, mahogany-colored cortices. The kidneys were smooth except for a large, irregular, gray-based cortical scar in the upper pole of the right kidney. The cortices were thickened, possessed distinct vascular markings and were sharply demarcated from normal pyramids. The pelves and the renal arteries were grossly normal. The bladder was not remarkable.

The fallopian tubes and the ovaries were bound to the fundus of the uterus by dense fibrous adhesions, which contained many small, soft and pseudofluctuant nodules. Some of the nodules contained yellowish gray to green purulent matter, while others were filled with caseous material. The uterus was enlarged, and there was a single whorled, densely fibrous circumscribed nodule in the fundus. The endometrium of the cavum uteri was largely replaced by patches of pale yellow material that was cheesy and granular. The cervical endometrium was grayish pink, smooth and boggy. The cervix was boggy and about twice the usual size. The surface was dull, dirty reddish gray to green and possessed large and small superficial areas of ulceration and erosion. The vagina and external genitalia were normal.

In the gastrointestinal tract a small esophageal diverticulum was adherent to the main left lower bronchus. The serosal surfaces of the stomach, small intestine and large bowel were covered with and bound together by moderately dense fibrous adhesions. The retroperitoneal nodes were enlarged and contained either caseous material or thick, creamy purulent matter.

The brain weighed 1,080 Gm. At a point beneath the tip of the right temporal gyrus the middle cerebral artery was occluded by a large, firm, adherent mass of old blood, and that portion of the right cerebral hemisphere which was supplied by this artery was discolored, soft and mushy.

The twelfth thoracic vertebra was collapsed, and in the region of this vertebra the spine was abnormally mobile. The remnants of the collapsed vertebra contained thick, creamy yellow purulent material. The bony trabeculae were soft, friable and necrotic. There was a soft swelling beneath the spinous ligaments with extension of the purulent material into the paravertebral soft tissues and beneath the head of the right psoas muscle.

Microscopic Observations. In the heart there was an old, acellular fibrous thickening of the epicardium, and the myocardium was extensively infiltrated with fat. In the lungs there was an old, densely fibrous thickening of the pleura, which contained a few scattered lymphocytes and plasma cells. There were numerous small areas of fibrous septal thickening and alveolar replacement. Several of the large arteries and veins in and about these areas contained organized and recanalized thrombi. No histologic evidence of tuberculosis was found.

The liver showed an old fibrous thickening of the capsule. The lobular arrangement of the liver cells was normal. The liver cells about the dilated and congested central veins were atrophied and fibrosed, while peripherally they were fatty. The sinusoids were dilated. The Kupffer cells were unusually prominent and contained large granules of golden brown pigment. The portal zones were moderately and diffusely infiltrated with lymphocytes, and though the small bile ducts were increased in number, their lining epithelium was normal and they contained no pigment. No portal fibrosis was observed. Sections stained for iron were remarkable because of the virtual absence of pigment giving a positive reaction for iron, only a rare Kupffer cell contained any iron pigment. In the pancreas the acinar and islet tissues were normal, but there was a slight increase in the interlobular connective tissue. A large interlobular vein contained an old and recanalized thrombus. Stains for iron gave negative results. In the left adrenal gland there was a large tubercle which had a central area of caseous necrosis and was surrounded by a broad zone of tuberculous granulation tissue containing several tuberculous giant cells.

The glomerular tufts in the kidneys were compact, cellular and mildly fibrotic and almost filled the glomerular spaces. In a few of the glomeruli there were fibrous adhesions between the tufts and the capsule. The lining epithelium of the convoluted tubules and the ascending loops of Henle were packed with great masses of golden brown pigment. These tubules showed varying degrees of degeneration and desquamation of the epithelium, as well as focal areas of regeneration and metaplasia. The collecting tubules exhibited varying degrees of cellular edema and degeneration and were made conspicuous by the complete absence of pigment in their lumens or lining epithelium. Several small interlobular arteries and veins and a large artery in the right kidney contained old organized and recanalized thrombi. Distal to the thrombosed large artery there was severe ischemic fibrosis of the parenchyma. Both pelves were fibrous and infiltrated with chronic inflammatory cells, in both kidneys there were small areas of healed pyelonephritis.

The structure of the fallopian tubes was replaced by tuberculous granulation tissue and areas of caseous necrosis. The cervix and cervical mucosa were densely fibrous and severely ulcerated. All of these structures were infiltrated with chronic inflammatory cells, epithelioid cells and tuberculous giant cells.

The para-aortic and hepatic lymph nodes were fibrocaseous and loaded with epithelioid and tuberculous giant cells.

There was extensive fibrosis of the marrow of the collapsed vertebra with caseous necrosis of the bone and fibrous marrow. Other sections exhibited normal erythroid and myeloid activity. Megakaryocytes were noticeably reduced in size and number.

SPECIAL DIAGNOSTIC METHODS

Samples of the patient's venous blood were drawn without hemostasis into a clean dry syringe and were immediately defibrinated with glass beads. A control sample of blood from a normal subject of the same blood group was treated in a like manner. Samples, measuring 10 cc., of the patient's and of the normal defibrinated blood were equilibrated in tonometers with 90 per cent oxygen and 10 per cent carbon dioxide at room temperature for fifteen minutes. These samples were then centrifuged at the same speed and the serum observed for hemolysis. The patient's blood showed definite hemolysis, whereas the normal blood showed no hemolysis.

Samples of the patient's and the normal defibrinated blood were centrifuged and the cells and serum separated. The cells were washed three times with physiologic solution of sodium chloride and a 5 per cent suspension of cells in

the solution of sodium chloride prepared. Samples of 1 cc of suspension of patient's cells were centrifuged, the solution of sodium chloride discarded and the cells resuspended in 1 cc both of patient's serum and of normal serum. Samples of the suspension of normal cells were similarly suspended in patient's serum and in normal serum. Another set of the four mixtures was prepared, differing only in that both the patient's serum and the normal serum had been acidified by the addition of 0.05 cc of third-normal hydrochloric acid to 0.95 cc of serum before the cells were resuspended in these serums. All of the tubes were then incubated for one hour at 37.5 C. Mixing was assured by gentle rocking of the tubes every ten minutes. At the end of this period of incubation the tubes were centrifuged and the serum observed for hemolysis. None of the tubes containing

*Comparison of Blood from Patient and from a Normal Person, Based on
Special Diagnostic Methods*

Treatment of Serum	Degree of Hemolysis	
	Patient's Red Blood Cells	Normal Red Blood Cells
Unaltered normal serum	+	0
Unaltered patient's serum	+	0
Acidified normal serum	+++	0
Acidified patient's serum	+++	0
Heat inactivated normal serum		
Acidified	0	0
Unacidified	0	0
Heat inactivated patient's serum		
Acidified	0	0
Unacidified	0	0

One cubic centimeter of a 5 per cent suspension of washed erythrocytes in physiologic solution of sodium chloride was centrifuged, the salt solution discarded and the erythrocytes resuspended in 1 cc of serum. The acidified serum was made by adding 0.05 cc of third normal hydrochloric acid to 0.95 cc of serum. Heat-inactivated serum was heated to 56 C for 30 minutes.

Treatment of Blood	Degree of Hemolysis	
	Patient's Defibrinated Blood	Normal Defibrinated Blood
Equilibrated in a tonometer for 15 minutes at room temperature with 90 per cent oxygen and 10 per cent carbon dioxide	+++	0
Equilibrated in a tonometer at room temperature with room air	+	0

normal cells showed hemolysis. All of the tubes containing patient's cells showed hemolysis. The tubes containing acidified serum and patient's cells showed considerable hemolysis, those containing unacidified serum and patient's cells showed moderate hemolysis. This study was repeated, with the same results.

These studies showed that the patient's and the normal serum contained some factor necessary for hemolysis and that only the patient's cells would be hemolyzed by this factor. It was also evident that the p_H of the serums affected the degree of hemolysis which was greater with the lower p_H .

Both the normal and the patient's serum were heated to 56 C for thirty minutes. Samples of acidified and unacidified heated serums were then added to the patient's and to normal washed red cells. None of the mixtures caused hemolysis of either the patient's or the normal cells. This test was interpreted as indicating that the substance responsible for the hemolysis of the patient's red cells was thermolabile (table).

Though there was no history of hemoglobinuria following exposure to cold and even though the patient's serologic reactions for syphilis were negative, the blood was studied for the presence of cold agglutinins by the Donath-Landsteiner test, as described by MacKenzie.⁷ The results were negative. Red cells of patients with the Marchiafava-Micheli syndrome may show slight to moderate hemolysis on standing alone and may, therefore, give a false positive Donath-Landsteiner reaction. To interpret the reaction as positive, it is essential that there be hemolysis of normal red cells by the serum of the patient being tested for cold agglutinins. This excludes the possibility of the hemolysis being due to abnormalities in the red cells themselves.

Despite the confirmatory laboratory evidence obtained from these tests, which indicated that the hemolytic anemia was of the Marchiafava-Micheli type, the patient excreted urine that was entirely normal and that gave no reaction to benzidine during the first two weeks in the hospital. Accordingly, an *in vivo* attempt to produce hemoglobinuria was made by acidification with ammonium chloride.

The patient was given 30 grains (1.94 Gm) of enteric-coated ammonium chloride during the first twenty-four hours, but no hemoglobinuria occurred. Sixty grains (3.88 Gm) was given during the next twenty-four hours, and at the end of this period the morning urine was rich chocolate-brown and gave strongly positive reactions with benzidine in dilutions as low as 1:10,000. This urine contained no red cells.

Although no further ammonium chloride was given, the patient continued to excrete hemoglobin in her morning urine for two weeks. During this period fractionated specimens of urine collected from 9 a m to 9 p m were benzidine negative, whereas those collected from 9 p m to 9 a m were always benzidine positive. Attempts were made to induce long periods of sleep during the daytime so that a specimen of urine might be studied on her awakening, but these were unsuccessful.

During the entire twenty-four hour period following the ether anesthesia incident to her operation, the patient showed hemoglobinuria, which, however, on the succeeding days occurred only in the morning samples. Again, the hemoglobinuria continued for two weeks.

After both the induced and the postanesthetic bout of hemoglobinuria, the patient's blood showed a drop in hemoglobin concentration of 10 to 15 per cent and an increase in reticulocytes from a previous level of 5 to 7 per cent to one of 15 to 24 per cent.

Transfusions of 500 cc of citrated blood were resorted to in order to maintain the patient's hemoglobin level. Slight to mild hemoglobinuria usually followed these transfusions.

COMMENT

This patient's condition is an example of the so-called atypical hemolytic anemias, which until recently did not accurately fit into any known classification.

Two outstanding features of this case need emphasis. The first is the presence of normal red cell fragility on repeated occasions. This phenomenon was the only factor which militated against the diagnosis of hemolytic icterioanemia. In the past it has always been unexplained and the lack of knowledge of its significance expressed by prefixing the

⁷ MacKenzie, G. M. Paroxysmal Hemoglobinuria, *Medicine* 8:159, 1929.

adjective "atypical" With the description of this new syndrome, many cases of this "atypical" form can be explained Thus, in the case of a patient who presents the clinical picture of hemolytic icterioanemia except for the presence of normal red cell fragility other types of chronic hemolytic anemia must be sought

This necessity leads directly to the second point Hemoglobinuria is not essential to the diagnosis of the Marchiafava-Micheli syndrome Ham has shown that chronic intravascular hemolysis occurs in these patients which may vary in severity over a period of months This produces hemoglobinemia, or free hemoglobin in the plasma Hemoglobinuria does not occur until the level of free hemoglobin in the plasma exceeds the renal threshold, which Ham found was usually above 30 mg per hundred cubic centimeters Thus the rate of hemolysis and, in consequence, the level of free plasma hemoglobin determine the presence or absence of hemoglobinuria It is important to note that the intravascular hemolysis has been shown to occur throughout the entire twenty-four hours and is merely exaggerated by sleep Obviously, then, the nocturnal occurrence of hemoglobinuria, associated with sleep, is a counterpart of increased nocturnal intravascular hemolysis For these reasons we concur in the suggestion of Ham that the descriptive name of this disease should more properly be chronic hemolytic anemia with paroxysmal nocturnal hemoglobinemia In this way the emphasis on hemoglobinuria will be reduced

The effect of splenectomy on this hemolytic mechanism is important from both the diagnostic and the theoretic standpoint This case exemplified both elements Before splenectomy hemoglobinuria occurred fairly frequently After splenectomy dark urine was passed only three times during a four and one-half year period The absence of hemoglobinuria undoubtedly postponed the making of a correct diagnosis In this way the true diagnosis of the condition in patients who are submitted to splenectomy under the mistaken diagnosis of "atypical hemolytic icterioanemia" may be made more difficult

The effect of splenectomy on the hemolytic mechanism in this disease is still discussed on theoretic grounds but deserves attention

Lowering of the p_H of the peripheral blood during sleep has been observed by several workers,⁸ and the increase in hemolysis due to slight changes in p_H of the cells of patients with Marchiafava-Micheli's disease has been shown It is felt that the changes in p_H exhibited by the peripheral blood do not necessarily reflect the shift in p_H in other regions of the body where the circulation is less active The spleen is designated as a "stasis" organ, and changes in p_H in the blood in this

⁸ Hastings, A. B., and Eisele, C. W. Diurnal Variations in Acid-Base Balance, *Proc Soc Exper Biol & Med* **43** 308, 1940 Kleitman, H. Sleep, *Physiol Rev* **9** 624, 1929 Ham⁵

area may be much greater than in the faster circulating peripheral blood. In 1 case reported by Ham⁹ the nocturnal element of the hemoglobinuria was noticeably diminished by splenectomy. In the case here reported there was a similar reduction in hemoglobinuria following splenectomy.

From a therapeutic standpoint, however, the fundamental abnormality of the red blood cells and the degree of anemia were not altered by splenectomy in 2 cases reported by Ham, as well as in our case.

Unexplained thrombocytopenia and leukopenia have been observed as fairly characteristic of this disease picture, whereas after splenectomy the platelet and leukocyte counts usually return to normal levels.⁹ The findings were similar in this case.

The diagnosis of this disease in the presence of frank hemoglobinuria is less difficult than when hemoglobinuria is absent or infrequent. In either case the absolute diagnosis depends on laboratory studies as outlined under the section on special methods. The patient's red blood cells must be shown to be abnormally sensitive to slight changes in p_{H} , and the absence of any hemolytic factor for normal cells in the patient's serum or plasma must be demonstrated. The production of hemoglobinuria by the administration of acid salts to those patients who do not show hemoglobinuria when first seen is dramatic but not without certain dangers. A period of increased hemolysis may be started which may not subside promptly. This was shown in our patient, who had nocturnal hemoglobinuria for two weeks after acidification, with a 10 per cent drop in the hemoglobin of the blood and considerable increase in reticulocytes. This procedure is not essential to the diagnosis, as already discussed. The *in vitro* studies, however, are essentially harmless.

No satisfactory therapeutic measure has as yet been found. The administration of alkaline salts was found to reduce the degree of hemoglobinemia while it was continued. On withdrawal of this therapy prolonged and severe hemoglobinemia and hemoglobinuria occurred.⁵

Splenectomy may reduce the frequency and severity of the hemoglobinuria, but it has not been possible to show, as yet, any reduction in the chronic intravascular hemolysis or the degree of anemia following this procedure.

In 1938 Scott, Robb-Smith and Scowen¹⁰ reported 2 cases of this disease and reviewed the pathologic observations in 7 of 28 cases collected from the literature. In their own cases and in those collected from the literature, they observed that the principal pathologic features consisted of vascular thromboses, hepatomegaly with central zonal necrosis, slight

⁹ Witts^{3a} Ham⁵

¹⁰ Scott, R. B., Robb-Smith, A. H. T., and Scowen, E. F. The Marchiafava-Micheli Syndrome of Nocturnal Haemoglobinuria with Hemolytic Anaemia, *Quart J Med* 7 95, 1938.

splenomegaly, with little deviation from normal hyperplastic bone marrow of an orthoplastic type, and hemosiderosis of an unusual distribution. The hemosiderosis was largely confined to the kidney, specifically to the convoluted tubules and the ascending loops of Henle, only traces of blood pigment were present in the other organs. Our findings are in accord with these observations.

The principal histopathologic features in our own and in other cases can be attributed to the effect of prolonged hemoglobinemia and vascular thromboses. Though fibrosis, thrombosis and hemosiderosis are frequent features of this disease, the histopathologic picture is not pathognomonic of the Marchiafava-Micheli syndrome. The tendency toward the development of vascular thrombi in patients with this disease was prominently displayed in this case and, as exemplified by the occlusion of the right middle cerebral artery, was directly responsible for the patient's death.

The patient's secondary disease was tuberculosis, and in view of the autopsy findings, it is probable that many of her earlier signs and symptoms (fever, asthenia, sweats, loss of weight and effusion into the serous cavities) can be attributed to an active phase of this infection. It is felt, however, that the tuberculosis was incidental to her primary disease and was of no etiologic significance. In no other case of this disease with autopsy has tuberculosis been shown.

SUMMARY

A patient with chronic hemolytic anemia was proved to have the Marchiafava-Micheli syndrome of paroxysmal nocturnal hemoglobinemia, despite the infrequent occurrence of the usual nocturnal hemoglobinuria.

This diagnosis was made possible by special *in vitro* diagnostic methods, described by a previous writer, which revealed the abnormal sensitivity of the patient's red blood cells to slight changes in p_H , such as occur during sleep.

Splenectomy was again shown to have no influence on the course or degree of the anemia but it did reduce the frequency and severity of the hemoglobinuria.

A complete necropsy revealed little other than the usual multiple vascular thrombi and histopathologic changes which can be attributed to the prolonged hemoglobinemia.

THE PRESENT STATUS OF NICOTINIC ACID

V P SYDENSTRICKER, M D

AUGUSTA, GA

During the two and a half years which have elapsed since Elvehjem and his associates¹ demonstrated the nutritional significance of nicotinic acid, much progress has been made in the clinical application of their discovery and much better insight into certain deficiency states has been gained. It was at once suspected that the importance of nicotinic acid in nutrition was related to its presence as the reactive fraction of the coenzymes diphosphopyridine nucleotide and triphosphopyridine nucleotide. Both coenzymes function in a number of dehydrogenating or oxidizing reactions, and the diphosphopyridine nucleotide may also act as a phosphate carrier. Their activity in the intermediate metabolism of dextrose is probably of the greatest clinical interest. The chemical reactions may be tentatively summarized. After the phosphorylation of hexose to hexose diphosphate and subsequent cleavage to triose phosphate, the pyridine nucleotides oxidize triose phosphate, losing oxygen, which is replaced by the oxidation of flavoprotein. Flavoprotein is in turn reoxidized by molecular oxygen, possibly derived from cellular heme. In the later stages of the utilization of dextrose reduced coenzyme I acts as a hydrogen donor in the conversion of pyruvic acid to lactic acid. These processes are continuous, and though it has been shown experimentally that the coenzymes can be reduced and regenerated many times, in the living cell it seems probable that they are eventually exhausted or rendered inactive unless there is adequate replacement. When energy is derived almost exclusively from carbohydrate or when there is for any reason an excessive demand for energy production the phosphopyridine nucleotides apparently are used up at a greatly increased rate. The various morbid states resulting from nicotinic acid deficiency may thus be thought of as chemical disturbances of cellular metabolism due to the failure of the coenzymes to function.

From the University of Georgia School of Medicine

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1 Elvehjem, C A, Madden, R J, Strong, F M, and Woolley, D W. Relation of Nicotinic Acid and Nicotinic Acid Amide to Canine Blacktongue, J Am Chem Soc **59** 1767, 1937

Up to the present it has been necessary to rely entirely on clinical observation for detection of nicotinic acid deficiency in man and for evaluation of its severity. Little is known of pathologic variations of the concentration of nicotinic acid in the blood or tissues or of the extent to which it is stored and excreted. Elvehjem² used the yeast fermentation method of Euler for the determination of coenzyme I (diphosphopyridine nucleotide) as an index of the nicotinic acid content of the blood and tissues of normal and nicotinic acid-deficient dogs. He was unable to demonstrate any significant reduction of the cozymase in the blood, brain or renal cortex of the acid-deficient animals, the liver showed marked depletion and the muscles significant but variable loss. Vilter, Vilter and Spies³ and Kohn and Bernheim⁴ estimated the coenzyme I in the blood of normal and of pellagrous persons, using the bacterial growth method of Lwoff and Lwoff. The results of the investigations by these two groups were at variance. The Vilters and Spies found a great reduction of coenzyme in the blood of pellagrins in relapse and observed a rapid increase after the administration of large doses of nicotinic acid. Kohn and Bernheim⁴ and Kohn⁵ could demonstrate no significant difference in the cozymase content of the blood of normal persons and of pellagrins but did observe that the concentration in the blood of both types of persons was increased after nicotinic acid therapy was instituted. My own observations confirmed those of Kohn. Ritsert⁶ used a colorimetric method for the quantitative determination of nicotinic acid in the blood, this was modified by Pearson⁷ and by Briggs,⁸ who has succeeded in eliminating color due to substances other than nicotinic acid. Briggs found that blood normally contains from 3 to 3.5 micrograms of nicotinic acid per cubic centimeter, these values are somewhat lower than those obtained by Swaminathan,⁹ Ritsert or Pearson but are probably more accurate. Briggs did not observe marked lowering of nicotinic acid in the blood of pellagrins.

2 Elvehjem, C. A. The Biological Significance of Nicotinic Acid, *Bull. New York Acad. Med.* **16** 173, 1940.

3 Vilter, R. W., Vilter, S. P., and Spies, T. D. Relationship Between Nicotinic Acid and a Coenzyme (Cozymase) in Blood of Pellagrins and Normal Persons, *J. A. M. A.* **112** 420 (Feb. 4) 1939.

4 Kohn, H. I., and Bernheim, F. Blood V-Factor (Coenzyme) in Normal and Pathologic Subjects, *J. Clin. Investigation* **18** 585, 1939.

5 Kohn, H. I. The Concentration of Coenzyme-Like Substances in Blood Following the Administration of Nicotinic Acid to Normal Individuals and Pellagrins, *Biochem. J.* **32** 2075, 1938.

6 Ritsert, K. Zur quantitativen Nicotinsäure- und Nicotinsäureamid-Bestimmung im Harn, in Geweben und im Blut, *Klin. Wchnschr.* **18** 934, 1939.

7 Pearson, P. B. Nicotinic Acid of Mammalia, *J. Biol. Chem.* **129** 491, 1939.

8 Briggs, A. P. Personal communication to the author.

9 Swaminathan, M. Chemical Method for the Estimation of Nicotinic Acid in Biological Materials, *Indian J. M. Research* **26** 427, 1938.

but found increased amounts in the blood of both normal and pellagrous persons after the ingestion of nicotinic acid. The clinical value of the method remains to be determined, since the weight of evidence at present is against the likelihood that clinical manifestations of deficiency are accompanied by significant lowering of the nicotinic acid in the blood. Elvehjem² suggested that marked lowering of the concentration of coenzymes in the blood, brain and renal cortex may be incompatible with life, and it follows that chemical evidence of deficiency must be sought elsewhere. Tests for the presence of nicotinic acid and its compounds in the urine offer considerable promise, since it is certain that these substances are excreted to some extent during health. Vilter, Spies and Mathews¹⁰ applied the method of Baumgarten¹¹ and of Karrer and Keller¹² to the colorimetric determination of nicotinic acid and its amide in the urine with some success, but the difficulty of eliminating other chromogens has limited its usefulness. Vilter, Vilter and Spies³ used the bacterial growth method of the Lwoffs and found that the V factor (a cohydrogenase) is much reduced in the urine of pellagrins in relapse, increasing rapidly after the administration of nicotinic acid. More recently Fraser, Topping and Sebiell¹³ tried the bacterial growth method of Knight as modified by Koser, Dorfman and Saunders¹⁴ in the assay of urine of animals with experimental blacktongue. They observed a significant relation between the clinical manifestations of the disease and the excretion of growth-promoting substances (nicotinic acid) in the urine. They also found marked diminution of urinary excretion of nicotinic acid before clinical signs of blacktongue could be recognized and the corollary, increased excretion before signs of improvement could be noted. If this method of recognition of nicotinic acid deficiency proves applicable to clinical investigation it will be a timely diagnostic aid.

Up to the present, nicotinic acid, nicotinic acid amide and sodium nicotinate have been the substances extensively used in the treatment

10 Vilter, S. P., Spies, T. D., and Mathews, A. P. A Method for the Determination of Nicotinic Acid, Nicotinamide and Perhaps Other Pyridine-Like Substances in Human Urine, *J. Biol. Chem.* **125** 85, 1938.

11 Baumgarten, P. Degradation of Pyridine to Glutaconic Dialdehyde. II. N-pyridinium Sulfonic Acid, *Ber. d. deutsch. chem. Gesellsch.* **59** 1167, 1926.

12 Karrer, P., and Keller, H. Eine kolorometrische Bestimmung des Nicotinsäure-Amide, *Helvet. chim. acta* **21** 463, 1938.

13 Fraser, H. F., Topping, N. H., and Sebiell, W. H. The Assay of Urine in Canine Blacktongue by the Use of *Shigella paradysenteriae* (Sonne), *Pub. Health Rep.* **53** 1836, 1938.

14 Koser, S. A., Dorfman, A., and Saunders, F. Nicotinic Acid as an Essential Growth Substance for Dysentery Bacilli, *Proc. Soc. Exper. Biol. & Med.* **38** 311, 1938.

of the deficiency in human beings, and it is likely that no compounds will be found to be more effective. Numerous pyridine and several pyrazine compounds have been tested for their potency in treatment of blacktongue and of human pellagra. Woolley, Strong, Madden and Elvehjem¹⁵ found that only the pyridine compounds capable of conversion into nicotinic acid or its amide were effective in treatment of blacktongue, while the monocarboxylic and the 2,3-dicarboxylic acid derivatives of pyrazine had about one-tenth the curative value of nicotinic acid. Spies and his collaborators¹⁶ obtained analogous results with pyrazine compounds in the treatment of pellagra but found that pyrazine monocarboxylic acid and pyrazine 2,3-dicarboxylic acid were also potent in doses of 500 to 800 mg daily. In common with other vitamins, the toxicity of nicotinic acid and of the amide and sodium salt is low. Animals show no untoward effects from amounts tremendously greater than those necessary in therapy,¹⁷ no vasomotor or cardiac disturbances have been noted in the animals used for test purposes. In human subjects nicotinic acid and sodium nicotinate given orally or parenterally may cause marked vasodilatation with elevation of the surface temperature and subjective itching and burning of the lips, pharynx and skin. Occasionally tachycardia with either mild elevation or depression of blood pressure may occur. A few patients complain of substernal distress and dyspnea. Twice I have seen intense erythema and vomiting during the intravenous administration of dilute solutions of sodium nicotinate. Two other patients had marked edema of the hands accompanied by localized erythema and severe burning and prickling confined to the palms and fingers without general vasodilatation. The general flushing reactions are commonly attributed to saturation with the vitamin but occasionally occur after the first administration of it to patients obviously deficient. Nicotinic acid amide has not been observed to produce vasomotor effects. A phase of activity of nicotinic acid which has received little attention is its effect on the secretion of hydrochloric acid. In normal subjects and in many with deficiency doses of 100 to 120 mg cause an increase in the secretion of hydrochloric acid by the stomach of the same order as that produced by 1 mg of

15 Woolley, D W, Strong, F M, Madden, R J, and Elvehjem, C A. Anti-Blacktongue Activity of Various Pyridine Derivatives, *J Biol Chem* **124**: 715, 1938.

16 Vilter, S P, Bean, W B, and Spies, T D. Further Observations on the Effect of 2,6-Dimethyl Dimicotinic Acid and Dimicotinic Acid on Pellagrins in Relapse and on Normal Persons, *South M J* **31** 1163, 1938. Bills, C E, McDonald, F G, and Spies, T D. Antipellagic Action of Pyrazine-2,3-Dicarboxylic Acid and Pyrazine Monocarboxylic Acid, *ibid* **32** 793, 1939.

17 Chen, K K, Rose, C L, and Robbins, E B. Toxicity of Nicotinic Acid, *Proc Soc Exper Biol & Med* **38** 231, 1938. Unna, K. Studies on the Toxicity and Pharmacology of Nicotinic Acid, *J Pharmacol & Exper Therap* **65** 95, 1939.

histamine phosphate¹⁸ It is possible that this effect has bearing on the actual cure of chronic pellagra

Pellagra is a polyavitaminosis in which deprivation of nicotinic acid is only one factor, evidence of deficiency of thiamine and riboflavin is seldom absent, and some grade of deficiency of ascorbic acid is frequent Since it seems necessary to reserve the term pellagra for the syndrome presenting a specific type of dermatitis, many of the manifestations of nicotinic acid deficiency cannot properly be called pellagrous There are only two methods of clinical analysis of the problem The more accurate is the observation of patients maintained on a diet extremely poor in all vitamins but amply supplemented with all but nicotinic acid The second is the administration of the single vitamin under circumstances which would seem to warrant the assumption that a specific deficiency is present Even with such imperfectly controlled observations it has become evident that there are a number of manifestations of nicotinic acid deficiency and various mechanisms which may produce them It also seems highly probable that the tissue changes which characterize typical pellagra result from prolonged partial deficiency of the vitamin, while severe acute deprivation produces quite different effects As in all avitaminoses, the defect of nutrition may result from inadequate intake or from poor absorption or failure of utilization when adequate amounts of the vitamin are ingested

It is trite and perhaps superfluous to state that a poor diet is the most important single factor in the production of all grades of nicotinic acid deficiency, but the significance of the composition of diets is still not appreciated by many practitioners of medicine and perhaps a comparable proportion of dietitians The idea is still prevalent that dietary inadequacy implies semistarvation, it is extremely difficult to implant the fact that a diet may have excellent caloric value but produce severe nicotinic acid deficiency because it necessitates excessive derivation of energy from carbohydrate The adequacy of the vitamin intake is directly related to the proportion of calories derived from carbohydrate and to the metabolic demands of the body

Failure of absorption of nicotinic acid from natural food sources is common in various disorders of the gastrointestinal tract Persistent vomiting or diarrhea from any cause may precipitate the signs and symptoms of avitaminosis The absence of free hydrochloric acid from the stomach seems to interfere with the digestive processes necessary for the extraction of nicotinic acid from food Achlorhydria is common in all chronic avitaminoses, and in pellagra it seems likely that this disturbance of gastric function may first be due to chronic partial deficiency of nicotinic acid and then contribute largely to the persistence

18 Svdenstricker, V. P., and others Treatment of Pellagra with Nicotinic Acid, *South M J* **31** 1155, 1938

of the syndrome. Edema of the gastric and intestinal mucosa, such as occurs in heart failure, nephritis and portal obstruction, interferes with the absorption of all vitamins. Evidences of deficiency are frequent in various diseases of the liver, particularly in portal cirrhosis, chronic passive congestion and fatty degeneration. It is likely that in such conditions utilization of nicotinic acid is interfered with by disturbance of hepatic function. Whether there is failure of synthesis of nicotinic acid amide or of the phosphopyridine nucleotides or whether there is simply inadequate storage of these substances cannot yet be determined.

Severe grades of deficiency with rapidly developing pellagrous lesions may result from a sudden increase in metabolic activity. Pregnancy, acute hyperthyroidism, fever and unusual physical exertion are common causes of such metabolic stress. Similar clinical pictures may be produced when patients are maintained for a number of days on solutions of dextrose given intravenously or when large increments of carbohydrate and insulin are added to a regimen for persons with diabetes. Not infrequently the substitution of alcohol for food precipitates acute pellagra. In all these conditions it is likely that increased coenzyme activity results in the actual using up of all available nicotinic acid.

Since it can be assumed with some confidence that compounds of nicotinic acid are essential for the nutrition of every living cell, it seems highly probable that the variety of manifestations of deficiency depends on the sensitiveness of different tissues to varying grades of metabolic disturbance. When there is prolonged moderate lack of the vitamin, functional disturbances may be slight for a considerable time, eventually they become severe, and finally anatomic changes occur. When deficiency is severe or acute, profound functional disorders may be produced so rapidly that tissue changes do not have time to develop. All intermediate combinations of functional and anatomic effects of deficiency may be observed.

In the chronic partial deficiency of nicotinic acid that eventually results in endemic pellagra, mild psychic disturbances are almost always the first evidence of disease. Neurasthenic complaints of all sorts, forgetfulness, slight mental retardation or mild and transient delusional states may recur for months or even years¹⁹. Partial deafness may be the presenting symptom²⁰. Vague digestive disturbances with anorexia

19 Spies, T. D., Bean, W. B., and Stone, R. E. The Treatment of Sub-clinical and Classic Pellagra. Use of Nicotinic Acid, Nicotinic Acid Amide and Sodium Nicotinate with Special Reference to the Vasodilator Action and the Effect on Mental Symptoms, *J. A. M. A.* **111** 584 (Aug 13) 1938. Spies, T. D., Aring, C. D., Gelperin, J., and Bean, W. B. The Mental Symptoms of Pellagra. Their Relief with Nicotinic Acid, *Am. J. M. Sc.* **196** 461, 1938.

20 Selfridge, G. Eighth Nerve in Relation to Thiamine Chloride and Nicotinic Acid. Comparative Study, *Ann. Otol., Rhin. & Laryng.* **48** 419, 1939.

are likely to ensue, mild glossitis is apt to accompany such symptoms. The food intake is apt to be reduced in an effort to mitigate indigestion or as a result of progressive lack of appetite. With increasing malnutrition glossitis proceeds to atrophy of the lingual papillae, functional or anatomic changes in the gastric mucosa result in achlorhydria. Diarrhea may be initiated by the presence of undigested food or as a result of atrophic changes in the intestinal mucosa preventing normal absorption of fluid. Progressive psychic deterioration may further limit the ingestion of food. At any time dermatitis may appear, frequently but not necessarily precipitated by some type of trauma. Infection is apt to occur in the mouth, esophagus, rectum or vagina, probably from disturbance of normal cellular defense mechanisms. Finally, delirium, dementia, stupor or the encephalopathic syndrome²¹ indicates the maximal grade of deficiency of nicotinic acid compatible with life. The full development of pellagra may require a few months or many years. In the great majority of instances the process is frequently, sometimes permanently, interrupted by accidental improvement in the diet, by diminished metabolic demands or by the administration of curative substances. Occasionally irreversible changes are produced in the gastrointestinal mucosa, so that patients remain potentially pellagrous with enormous requirements for nicotinic acid. More often there is permanent damage to the brain, with dementia.

When rapid, severe depletion of nicotinic acid is brought about by maintenance for several days on dextrose solutions given intravenously or by acute infection with much fever and inadequate feeding or by severe alcoholism, psychic disturbances are seldom lacking, confusion or delirium is the common pattern. Severe glossitis is constant and is apt to be accompanied by stomatitis and esophagitis, secondary infection in the mouth and esophagus with fungi or Vincent's organisms is frequent. Occasionally the bullous or rapidly necrotizing types of symmetric dermatitis develop with amazing speed.

A maximal deficiency of nicotinic acid is suspected of being the cause of the atypical psychotic states described by Cleckley and others²² and the encephalopathy reported by Jolliffe and others²¹. It is likely that delirium tremens and postalcoholic stupor belong in the same category. Profound clouding of consciousness grading into complete stupor, cogwheel rigidities and primitive grasping and sucking reflexes are characteristic. Relatively few patients have shown the lesions of pellagra, and it is believed that this encephalopathic syndrome repre-

21 Jolliffe, N., Bowman, K. M., Rosenblum, L. A., and Fein, H. D. Nicotinic Acid Deficiency Encephalopathy, *J. A. M. A.* **114** 307 (Jan 27) 1940.

22 Cleckley, H. M., Sydenstricker, V. P., and Geeslin, L. E. Nicotinic Acid in the Treatment of Atypical Psychotic States Associated with Malnutrition, *J. A. M. A.* **112** 2107 (May 27) 1939.

sents the most severe and acute manifestation of nicotinic acid deficiency, developing too rapidly for tissue changes to occur. Looking back to the period preceding the use of liver extracts in the treatment of severe pellagra, one can be certain that encephalopathy induced by a deficiency of nicotinic acid was the common terminal event in endemic pellagra.

The response of all grades of nicotinic acid deficiency to specific treatment with the vitamin is rapid and usually complete, though it is seldom possible to predict the amount requisite for cure or for maintenance. The normal requirement is probably about 25 mg a day² and a few patients with mild endemic pellagra can be cured, though slowly, with this amount. If the intake is increased to 300 or 500 mg, the cure of glossitis, stomatitis and diarrhea is truly dramatic, seldom requiring more than two days, mild psychic disturbances disappear even more rapidly, and cutaneous lesions require from seven to fourteen days for complete resolution. In cases of severe pellagra 600 to 1,000 mg daily for three days is usually adequate for relief of all urgent symptoms. Because no advantage has been evident from the continuation of such large amounts of the vitamin, it has become customary to reduce the dose to 100 or 150 mg per day after improvement has begun. In treatment of the acute deficiencies best results have been obtained from large amounts of nicotinic acid given until the symptoms were controlled. The stuporous or encephalopathic patient may require 1,200 to 1,800 mg daily for four or five days, one with acute deficiency from ingestion of too much dextrose or alcohol may need as much. It is probably advantageous to give such large amounts of the vitamin in divided doses of not over 100 mg at intervals of an hour, to avoid loss of considerable quantities by excretion in the urine. When vomiting prevents the oral administration of nicotinic acid or when patients are stuporous or for other reasons entirely uncooperative, sodium nicotinate or nicotinic acid amide can be given by intramuscular or intravenous injection. When sodium nicotinate is given intravenously it should be well diluted with physiologic solution of sodium chloride and injected slowly, to avoid vasodilator reactions. It is my conviction that effects are obtained more rapidly when parenteral routes of administration are employed.

The amount of nicotinic acid required for maintenance is exceedingly variable and probably depends on the absorptive capacity of the gastric and intestinal mucosa and the functional integrity of the liver. Many patients with mild endemic pellagra are well maintained on 25 or 30 mg a day. The average requirement of those with longstanding deficiency is 100 mg. For persons with irreversible achlorhydria and with diarrhea due to structural changes in the colon the minimum may be 600 mg a day. The severe acute deficiency states do not produce lasting changes in the tissues and no maintenance after

cure is necessary unless there has been preexisting chronic pellagra. It must be remembered that nicotinic acid deficiency is probably always associated with riboflavin and thiamine deficiency and that the manifestations of these avitaminoses are apt to progress unless recognized and treated.

In summary, experimental and clinical evidence supports the theory that the nutritional significance of nicotinic acid depends on the part it plays as a component of the coenzymes diphosphopyridine nucleotide and triphosphopyridine nucleotide. In animals it has been shown that only relatively slight depletion of these compounds occurs even in severe nicotinic acid deficiency. No entirely satisfactory method of chemical diagnosis of this deficiency has been developed, it seems likely that determinations of the urinary excretion of nicotine acid promise to be more helpful than determinations of coenzymes or of nicotinic acid in the blood.

It is probable that the clinical manifestations of nicotinic acid deficiency are the result of disturbances of cellular nutrition when the available supply of nicotinic acid is insufficient for the adequate replacement of coenzymes. An important cause of rapid depletion of coenzymes is the excessive derivation of energy from carbohydrate. Since the cerebral neurons are highly sensitive to disturbances of their nutrition, it is not remarkable that psychic disturbances of various patterns are common in all types of nicotinic acid deficiency. The grade and nature of symptoms and signs of this deficiency are determined by the severity and duration of avitaminosis.

All known manifestations of deficiency of nicotinic acid are cured rapidly and usually completely by adequate specific therapy. It is not yet possible to predict the amounts of the vitamin necessary for cure or maintenance in every instance.

ELECTROCARDIOGRAPHIC STUDIES IN A CASE OF PERIODIC PARALYSIS

BERNARD STOLL, M D

Clinical Assistant in Medicine, Jewish Hospital

AND

SAMUEL NISNEWITZ, M D

Clinical Assistant in Cardiology, Jewish Hospital

BROOKLYN

Study of this rare disease has recently been stimulated by the discovery that the recurrent attacks of flaccid paralysis which characterize this condition are associated with a marked fall in the serum potassium and that the administration of potassium salts brings about rapid recovery from the attacks ¹

A review of the literature reveals a sparsity of observations on the electrocardiographic alterations induced by the disease. The papers of Janota and Weber ² and Zabriskie and Frantz ³ are the only ones, to our knowledge, which record electrocardiographic observations. These authors found lowering of the T waves during the paralytic episodes. It is our intention in this report to furnish additional data along these lines, as well as experimental observations on the effects of certain drugs.

REPORT OF CASE

B R, a man aged 25, came under our observation in February 1939. His family history was unknown to him in any detail, owing to the early death of his parents. Except for the development of thromboangitis obliterans in the right leg three years previously, he had been in good health.

The present illness began rather suddenly on Feb 24, 1939. On awakening that morning he found himself unable to get up because of almost complete loss of motor power from the neck down.

1 (a) Aitkin, R S, Allott, E N, Castledon, L I M, and Walker, M. Observations on a Case of Familial Periodic Paralysis, *Clin Sc* **3** 47 (July) 1937. (b) Ferrebee, J W, Atchley, D W, and Loeb, R F. A Study of the Electrolyte Physiology in a Case of Familial Periodic Paralysis, *J Clin Investigation* **17** 504 (July) 1938. (c) Pudenz, R H, McIntosh, J F, and McEachern, D. The Role of Potassium in Familial Periodic Paralysis, *J A M A* **111** 2253 (Dec 17) 1938.

2 Janota, O, and Weber K. Die paroxysmale Lahmung. Eine Studie über ihre Klinik und Pathogenese, *Abhandl a d Neurol, Psychiat, Psychol u Grenzgeb* **46** 1, 1928.

3 Zabriskie, E G, and Frantz, A M. Familial Periodic Paralysis, *Bull Neurol Inst New York* **2** 57 (March) 1932.

Physical examination revealed a well developed man of sthenic habitus, he was somewhat drowsy, was perspiring moderately and did not appear acutely ill

There was flaccid paralysis involving the trunk and the upper and lower extremities. The biceps and ankle jerks were absent, but the triceps and knee jerks were present. There were no pathologic reflexes and no sensory changes, and the cranial nerves were normal.

On auscultation, it was found that the cardiac rhythm was regular, except for an occasional dropped beat. There were no extrasystoles. The first sound at the apex was slightly dull. There were no murmurs, and the heart was not enlarged. The rate was 90 beats per minute, and the blood pressure was 130 systolic and 70 diastolic. The right dorsalis pedis and posterior tibial pulses were absent.

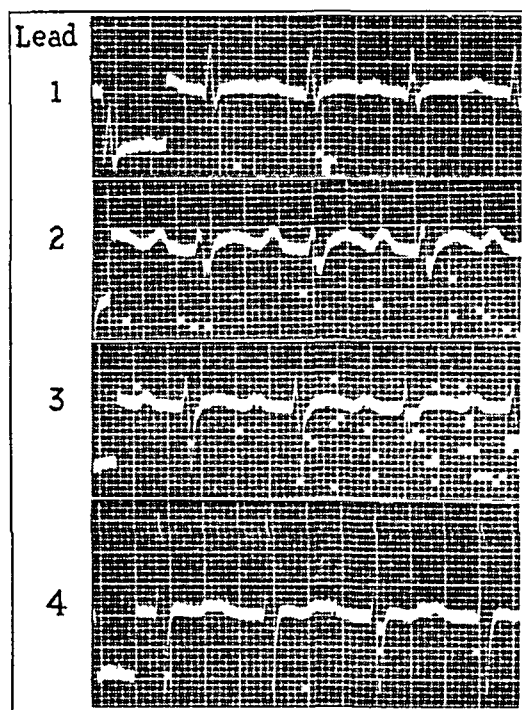


Fig 1—Electrocardiogram taken on March 7, during a moderately severe attack, at which time the serum potassium was 11 mg per hundred cubic centimeters. The electrocardiogram shows prolongation of auriculoventricular conduction and abnormalities of the T waves.

This attack of paralysis disappeared spontaneously in about five hours, with complete recovery of motor power, return of the lost reflexes and disappearance of the dropped beats.

Essentially similar attacks, the degree and site of motor weakness varying somewhat, have been observed since then. Most of these occurred in the early morning, especially if the patient had partaken of excessive food or fluids late the night before. Between attacks the patient felt perfectly well, and the physical examination revealed nothing abnormal.

Potassium chloride, in doses of 5 Gm administered orally, terminated attacks within an hour when taken promptly after the onset of symptoms. When the medication was delayed recovery was less rapid. A nightly maintenance dose of 5 Gm of potassium chloride was effective in keeping the patient free of attacks.

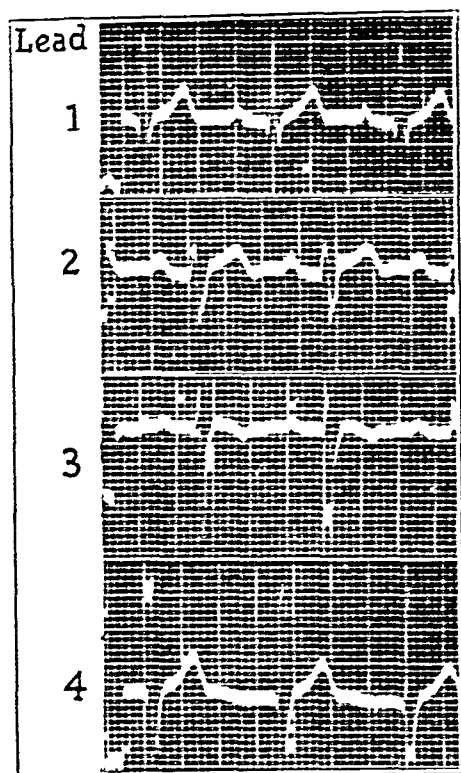


Fig 2—Electrocardiogram taken on March 9, forty-eight hours after recovery from paralysis. There are no significant abnormalities.

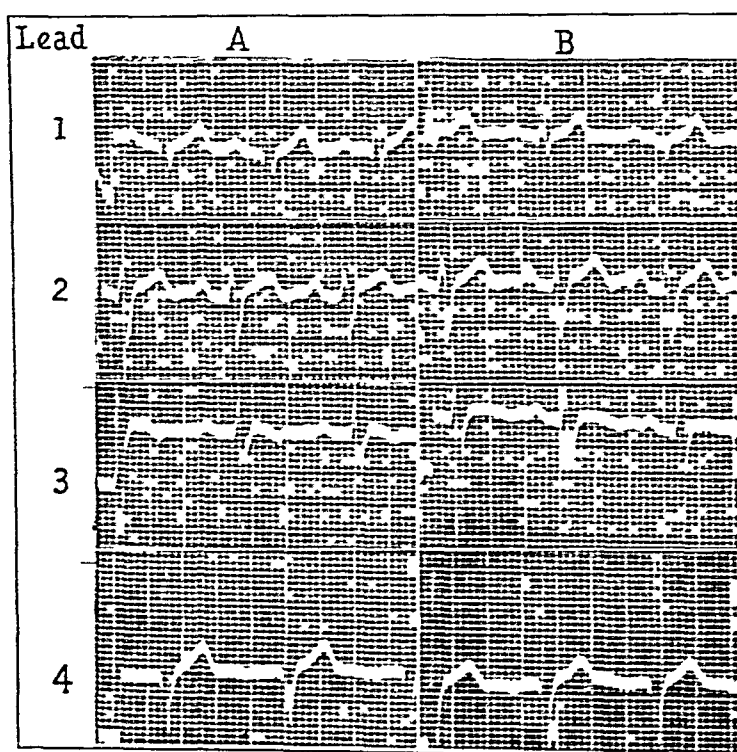


Fig 3—Electrocardiograms taken on March 19, during an interval when the patient was free from attacks of paralysis. A, before exercise, B, after exercise.

Foods rich in potassium, taken at bedtime, also prevented attacks. On one occasion 25 mg of mecholyl chloride (acetylbetamethylcholine hydrochloride), given subcutaneously, resulted in partial return of the reflexes in about ten minutes, although the paralysis was not abolished.

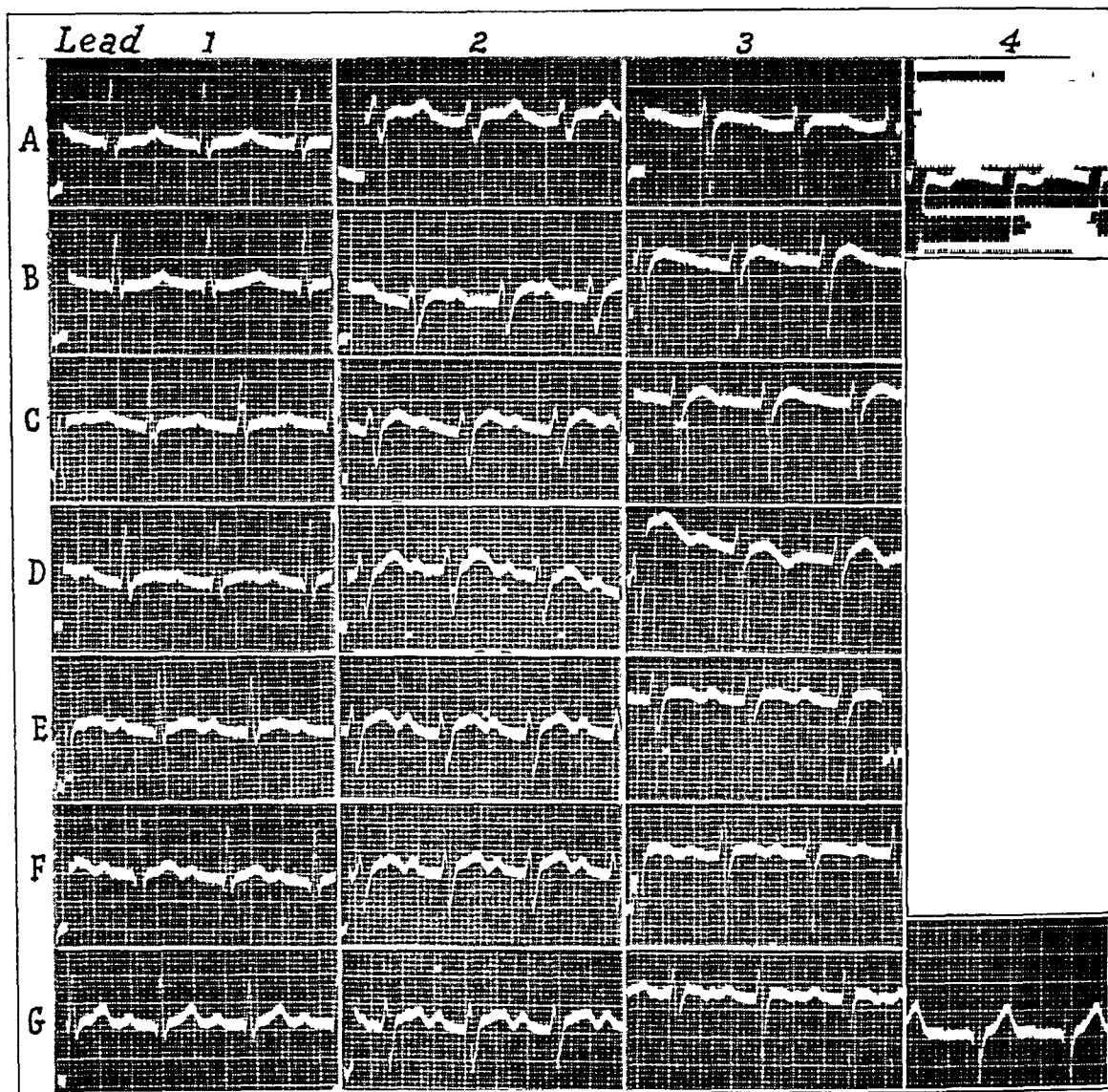


Fig 4—Serial tracings taken on June 23, during a severe attack of paralysis, before and at short intervals after the administration of potassium chloride. A, 8 45 a m, changes similar to those in figure 1. Five grams of potassium chloride was administered at 9 00 a m, B, 9 18 a m, C, 9 33 a m, D, 9 45 a m, E, 10 15 a m, F, 11 00 a m, and G, 11 35 a m. These tracings show a gradual return to almost normal limits in two and one-half hours after administration of potassium chloride. There was a concomitant improvement in the paralysis. Slight weakness in the upper extremities was still present at 11 35 a m.

Laboratory Data—Chemical analysis of blood taken during an attack revealed potassium 11 mg per hundred cubic centimeters (Kaye method, normal 16 to 20 mg per hundred cubic centimeters), calcium 10.7 mg, magnesium 17 mg and total

base 148.5 milliequivalents. Similar determinations one and one-half hours after spontaneous recovery showed potassium 16 mg per hundred cubic centimeters, calcium 10.7 mg, magnesium 2.0 mg and total base 150.5 milliequivalents.

Studies on the excretion of creatine and creatinine on three specimens of urine collected over successive twenty-four hour periods revealed creatine 0.2, 0.34 and 0.1 Gm and creatinine 0.86, 1.6 and 1.4 Gm, respectively (Benedict method).

The Wassermann reaction of the blood, the results of urinalysis and the blood counts were normal.

A fluoroscopic examination of the heart and lungs showed nothing abnormal.

The first electrocardiogram was taken on March 7 at 9 a.m., during a moderately severe attack of paralysis, at which time the serum potassium was 11 mg per hundred cubic centimeters. The tracing showed sinus tachycardia, rate 100 beats per minute, extreme prolongation of the auriculoventricular conduction (PR interval

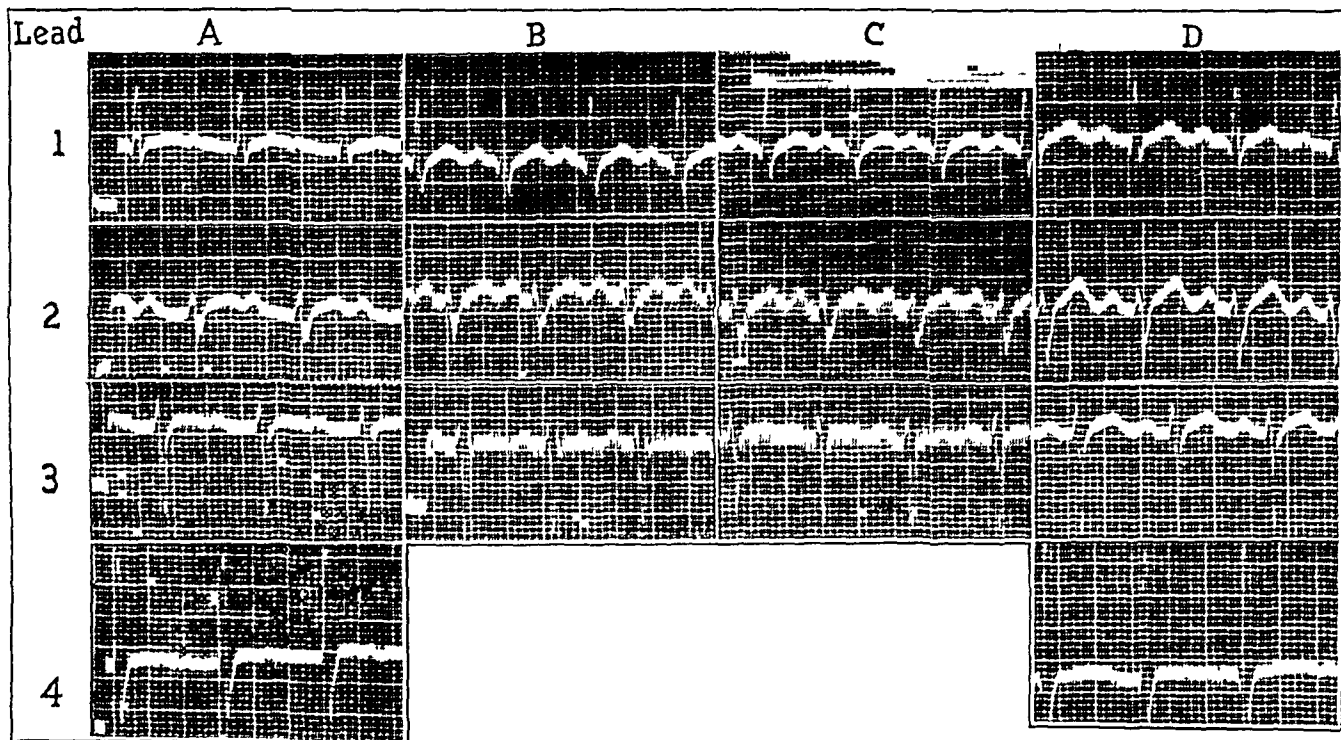


Fig 5—Electrocardiograms taken during an attack of paralysis on August 28. A, 7:40 a.m., previous to the administration of any drug. B, 1/50 grain (13 mg) of atropine sulfate was given subcutaneously at 7:56 a.m. This dose was repeated at 8:35 a.m. A tracing taken at 8:55 shows a PR interval of 0.18 second and an increase in the height of the T waves. C, 25 mg mechoyl chloride was given subcutaneously at 9:00 a.m. Repeated tracings taken for one-half hour showed no further changes. D, 5 Gm of potassium chloride was given at 9:30 a.m. This tracing was taken at 10:00 a.m., at which time there was complete recovery from paralysis.

0.28 second), and abnormalities in the T waves (flat in lead I, low and broad in leads II and III and small and inverted in lead IV [fig 1]).

The tracings made on March 9 and 19, when the patient was free of attacks, showed no significant abnormalities (figs 2 and 3A and 1B).

During another, somewhat more severe, attack of paralysis occurring on June 23, the electrocardiogram showed similar, though somewhat more marked, changes rate 110 beats per minute, PR interval 0.32 second, flat T waves in the conventional leads, a small and inverted T wave in lead IV and upward curving of the ST segments. Serial tracings were then made after administration of potassium chloride by mouth. It was observed that there was a gradual return of the electrocardiogram to practically normal limits within two and one-half hours (fig 4). There was a concomitant improvement in the paralysis, so that at the end of this period there was only slight weakness of the upper extremities.

On August 28, during a typical attack, electrocardiograms were taken before and after the administration of atropine sulfate, mecholyl chloride and potassium chloride. After the administration of atropine the PR interval returned to normal and the T waves became higher, approaching their normal configuration (fig 5). Twenty-five milligrams of mecholyl chloride given subcutaneously after the administration of the atropine, produced no further alteration in the electrocardiogram (fig 5).

COMMENT

Lowering of the serum potassium during the paralytic episodes of this disease and prompt recovery from attacks after the administration of potassium salts have recently been recorded. The studies in our case substantiate these observations.

We wish to stress in particular the striking electrocardiographic changes in our patient during the paralytic attacks. These changes consisted mainly of marked impairment in auriculoventricular conduction and flattening of the T waves.

Direct correlation between the height of the T waves and the level of serum potassium has been reported recently by Thomson⁴ in a case of Addison's disease and in cases of uremia. Also, in the experimental raising of the level of serum potassium in dogs by slow intravenous injection of potassium chloride, the first electrocardiographic change was found to be a marked increase in the height of the T waves (Winkler, Hoff and Smith⁵).

The abolition of the conduction defect and the tendency toward return to normal of the T waves after administration of atropine sulfate indicate that increased vagal tone is probably present during attacks. These effects have been noted clinically by Pudenz and associates,¹⁰ who reported that the bradycardia which occurred during their patient's attacks disappeared after the administration of atropine.

4 Thomson, W. A. R. Potassium and the T Wave of the Electrocardiogram, *Lancet* **1** 808 (April 8) 1939.

5 Winkler, A. W., Hoff, H. E., and Smith, P. K. Electrocardiographic Changes and Concentration of Potassium in Serum Following Intravenous Injection of Potassium Chloride, *Am J Physiol* **124** 478 (Nov) 1938.

Although we do not wish to speculate regarding the mechanism underlying these changes, we think it worthy of note that electrocardiographic abnormalities of such magnitude can be produced by disturbances of the electrolyte balance in the absence of demonstrable organic disease of the heart

SUMMARY

A typical case of periodic paralysis in which impairment in auriculo-ventricular conduction and abnormalities in the T waves of the electrocardiogram appeared during the paralytic episodes is reported

The relation of these changes to the level of serum potassium is discussed in some detail

These changes are partially abolished by the administration of atropine and completely disappear with the end of the paralytic attack, whether the termination is spontaneous or is induced by the administration of potassium salts

Mr Kaye and Mr Sobel, of the chemistry department of the Jewish Hospital, Brooklyn, performed the chemical analyses of the blood

PRECOCIOUS PUBERTY AND TUMORS OF THE HYPOTHALAMUS

REPORT OF A CASE AND REVIEW OF THE LITERATURE, WITH A
PATHOPHYSIOLOGIC EXPLANATION OF THE PRECOCIOUS
SEXUAL SYNDROME

LAURENCE M WEINBERGER M D

CHICAGO

AND

FRANCIS C GRANT M D

PHILADELPHIA

Though numerous endocrine disturbances occur with disease or tumors of the brain, none has a more intriguing interest or presents so challenging a problem with respect to its cause than precocious puberty

There is at present a widely believed theory that it is caused in some way by tumors of, or in the region of, the pineal body This association was first pointed out by Gutzeit,¹ but his case, viewed now, curiously does not appear to be a genuine instance of precocious puberty The clinical and diagnostic features of "pinealism" were described by Frankl-Hochwart,² who wrote

When one finds in a very young person (boy) along with the general symptoms of tumor, as well as the local signs of a lesion of the corpora quadrigemina, abnormal body growth, unusual growth of hair, adiposity, somnolence, premature genital and sexual development and, finally, intellectual maturity, one must think of a pineal tumor

In the same year, after an extensive study of the pineal body, Marburg³ came to the conclusion that it was a gland of internal secretion He propounded the hypothesis that the pineal body in some way inhibits sexual maturation in early life but that sexual development coincides

From the Neurosurgical Service and Laboratory of the Hospital of the University of Pennsylvania

1 Gutzeit, R Ein Teratom der Zirbeldruse, Thesis, Königsberg, E Erlatis, 1896

2 von Frankl-Hochwart, L Ueber Diagnose der Zirbeldrumentumoren, Deutsche Ztschr f Nervenhe **37** 455, 1909

3 Marburg, O Die Adipositas cerebialis, ein Beitrag zur Kenntnis der Pathologie der Zirbeldruse, Deutsche Ztschr f Nervenhe **36** 114, 1908-1909, Die Adipositas cerebialis, ein Beitrag zur Pathologie der Zirbeldruse, Wien med Wehnschr **58** 2617, 1908, Zur Kenntnis der normalen und pathologischen Histologie der Zirbeldruse, die cerebrale Adipositas, Arb a d neurol Inst a d Wien Univ **17** 217, 1908

with involution of the gland, which normally occurs about the time of puberty. This theory provided the stimulus for an enormous amount of physiologic experimentation dealing with pineal extirpations, implantations, and feedings, injections of pineal extracts and electric stimulation, as well as many histologic and comparative anatomic studies. Fifteen years of immense labor, resulting in more than three hundred papers, was critically reviewed by Krabbe,⁴ who trenchantly commented as follows:

We must point out that the hypothesis that the secretion [of the pineal gland] plays a role in the development of puberty is to date completely without significant evidence. One has very often the impression that the authors' desire to consider the organ in secretory function is greater than their critical judgment regarding their published researches.

For a number of years after Krabbe's summation, interest in the pineal body lay dormant, but it has lately been revived. Rowntree, Hanson and their co-workers⁵ claimed that pineal extracts injected into successive generations of rats produced by the fourth generation evidences of accelerated development of the gonads and the sexual accessories. They were unable to detect any differences in sexual development following pineal extirpations. Davis and Martin⁶ performed pineal-ectomies on rats and cats. In the former they saw no evidence of sexual precocity but claimed that they did so in cats. This opinion was based on observations on only 3 cats out of the 14 that survived the operation. It should be pointed out that these authors claimed the same result from pineal deprivation that Hanson and Rowntree claimed from excessive administration of pineal extract. Many workers in addition⁷ have performed the same experiments as Davis and Martin, with opposite results. Engel,⁸ investigating the endocrinologic aspects, found that pineal extracts possess an antagonism to gonadotropic substances.

4 Krabbe, K. H. The Pineal Gland, Especially in Relation to the Problem of Its Supposed Significance in Sexual Development, *Endocrinology* **7** 739, 1923.

5 Rowntree, L. G., Clark, J. H., Steinberg, A., and Hanson, A. M. The Biologic Effects of Pineal Extract (Hanson). Accruing Retardation in Growth and Accruing Acceleration in Development in Successive Generations of Rats Under Continuous Treatment with Pineal Extract, *Endocrinology* **20** 348, 1936. Einhorn, N. H., and Rowntree, L. G. Experimental Phases of the Pineal Problem, *ibid* **24** 221, 1939.

6 Davis, L., and Martin, J. Results of Experimental Removal of Pineal Gland in Young Mammals, *Arch Neurol & Psychiat* **43** 23 (Jan.) 1940.

7 Dandy, W. E. Extirpation of the Pineal Body, *J Exper Med* **22** 237, 1915. Exner, A., and Boese, J. Ueber experimentelle Extirpation der Glandula pinealis, *Deutsche Ztschr f Chir* **107** 182, 1910. Christea, G. Genital Organs and Pineal Gland, *Rev stunt med*, 1912, cited by Krabbe.⁴

8 Engel, P. Assay of Pineal Extracts, *Endocrinology* **25** 144, 1939.

While his work was confirmed by Fleischmann and Goldhammer⁹ and Fischer,¹⁰ other workers, such as Vinals,¹¹ Wade¹² and Malek,¹³ repeating the same experiments, came to the opposite conclusion

When one thus reviews the poorly controlled, divergent and contradictory studies on the pineal body made in recent years, one cannot but feel that Krabbe's laconic criticism is still applicable. The secretory nature of the pineal gland is still unproved, though some writers¹⁴ cling to the belief that it elaborates a substance affecting sexual development.

On the other hand, some clinicians studying cases of precocious puberty associated with pineal tumors have begun to doubt, on clinical grounds, the causal connection between the two.¹⁵ They have turned their attention to the hypothalamus, where destruction can invariably be demonstrated when the autopsies in cases of pineal tumors are carefully studied. Bing, Globus and Simon^{15a} pointed out in an analysis of all the collected cases of *pubertas praecox* associated with pineal tumors that in 70 per cent there were symptoms or signs referable to hypothalamic involvement. This observation is not astonishing when the anatomic relations of the pineal gland are recalled and when the large size or invasive characteristics of tumors of this region are considered. Aside from the purely pathologic and clinical facts, these observations are important because they hint at the possibility that precocious puberty when occurring with lesions of the central nervous system is a hypothalamic syndrome.

It would be unjustifiable to add still another clinical syndrome to this already overburdened structure did not much evidence, clinical,

9 Fleischmann, W, and Goldhammer, H. Nachweis einer oestrushemmenden Substanz in der Zirbeldrüse junger Rattenweibchen, *Klin Wchnschr* **13** 415, 1934

10 Fischer, O. Isolation and Biological Assay of Efficacious Fraction of Pineal Gland, *Arch internat de pharmacodyn et de therap* **59** 340, 1938

11 Vinals, E. Renforcement de l'action gonadotrope de l'urine de la femme gravide, par association avec le glande epiphysaire, *Compt rend Soc de biol* **119** 259, 1935

12 Wade, N. J. Studies on the Function of the Pineal Gland, *Endocrinology* **21** 681, 1937

13 Malek, S. A. On the Relationship Between the Epiphysis Cerebri and the Reproductive System, *J Anat* **73** 419, 1939

14 von Kup, J. Der Zusammenhang zwischen der Zirbel und den anderen endocrinen Drüsen, *Frankfurt Ztschr f Path* **50** 152, 1936. Calvet, J. L'epiphyse, etude embryologique, histophysiologique et anatomo-clinique, Paris, J. B. Bailliere et fils, 1937

15 (a) Bing, J. F., Globus, J. H., and Simon, H. *Pubertas Praecox*. A Survey of the Reported Cases and Verified Anatomical Findings, with Particular Reference to Tumors of the Pineal Body, *J Mt Sinai Hosp* **4** 935, 1938. (b) Gardiner-Hill, H. Abnormalities of Growth and Development. Clinical and Pathological Aspects, *Brit M J* **1** 1241, 1937. (c) Grinker, R. R. Hypothalamic Functions in Psychosomatic Inter-Relations, *Psychosom Med* **1** 19, 1939

pathologic and physiologic, point to the participation of the hypothalamus in sexual development and function. In a sense, then, it is not a new hypothalamic syndrome that is proposed, but we submit that precocious puberty is merely a rare variant of hypothalamic sexual disturbances, the reverse of the genital atrophies and sexual infantilism so well known to occur with disease of this region. It is true, this conception does not have the merit of being new, for since Berblinger's¹⁶ paper writers have spoken of "hypothalamic hypergenitalism" and "pineal hypergenitalism." It is probably more accurate, however, and more in keeping with the facts, to call precocious puberty a hypothalamohypophyseal syndrome because, as we shall show later, the two structures are linked as intimately in the control of sexual activities as they are in other functions which are better known. However, we shall use the term "hypothalamic" because of the primary structure attacked. Therefore attention is directed to the fact that *pubertas praecox* occurs with lesions of the hypothalamus and the third ventricle in which the pineal body is not affected. So far as association with tumors is concerned, cases of this condition are rare. In all, 15 cases have been recorded.

The case to be reported is an instance of precocious puberty accompanying a glioma of the third ventricle and the hypothalamus. Apart from the unusual clinical features, which we were able to investigate in considerable detail, the case is especially valuable for two reasons. First, so far as can be found in the literature, it is only the second case of precocious puberty occurring with a tumor of the central nervous system in which opportunity was found to make complete endocrinologic studies with modern technics; second, the patient survived an operation in which a large mass of the tumor was removed.

We shall attempt to show from a study of our own and similar cases, taken in conjunction with the knowledge gained in experimental endocrinology, that it is now possible to offer a reasonably valid pathophysiologic interpretation of precocious puberty when it occurs with a tumor of the central nervous system. Heretofore, the evidence offered to indicate that the hypothalamus is the critical structure involved was obtained from clinical and pathologic observations. While these are suggestive, the important physiologic link, up to the present lacking, is found in the endocrinologic studies made in these cases. On the basis of this knowledge, the explanation of the genesis of precocious puberty which we offer is as follows. Lesions of the posterior portion of the hypothalamus interrupt nerve pathways or interfere with mechanisms which normally inhibit and control the production and release of

16 Berblinger, W. *Der Glandula pinealis*, in Henke, F., and Lubarsch, O. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol. 8, pp. 681-759.

gonadotropic substances from the anterior lobe of the hypophysis. The excessive liberation of these pituitary substances stimulates the ovaries or the interstitial cells of the testes, as the case may be, to overproduction of their specific principles, the estrogenic and androgenic substances. The latter are the substances known to be responsible for the development of the secondary sexual characters. The proof of the hyperactivity of the anterior lobe of the hypophysis is found indirectly in the presence of abnormally large amounts of estrogenic and androgenic substances in the urine of patients with precocious puberty. The following case report and a resume of the experimental knowledge concerning the role of the hypothalamus and the hypothalamohypophyseal relations respecting sexual functions are offered in support of this conception.

REPORT OF CASE

W. K., a boy 7 years and 11 months of age, was referred to the University Hospital by Dr. C. Hayden Phillips, of Wilkes-Barre, Pa. The complaints, as stated by the parents, were vomiting, headache, mental dulling, unsteadiness of gait and an extraordinary physical growth and sexual development.

The child was delivered by instruments after a normal gestation. He weighed $7\frac{3}{4}$ pounds (3,415 Gm.) at birth. His early growth and development were normal. He sat up at the age of 5 months, walked at 11 months, cut his first tooth at 12 months and talked at 18 months. A bilateral herniorrhaphy was performed at the age of 19 months. He had none of the common infectious diseases of childhood. He started school at the age of 6 but spent two years in the first grade. His mother blames his failure to pass on some vague visual disturbance of which she said the boy complained. He was, however, considered to be perfectly normal until the onset of his present illness.

This was ushered in approximately one year before admission to the hospital by a sudden and violent attack of vomiting, followed by a period of torpor and deep sleep which lasted for several hours. After this attack he seemed well for a time, but a similar episode occurred two months later. The vomiting spells then began to increase in frequency, usually occurring at first in the evenings but later during the day. In the few months before admission they were occurring several times daily. During this time his vision slowly failed, and shortly before admission he was removed from school, mainly because of his inability to read printing, although his vomiting and nervousness also contributed to his removal. The "nervousness" manifested itself two or three months before admission in a tremor of the hands, which gradually became more marked so that the child had difficulty in holding or handling objects. Along with this, his gait became unsteady, staggering and stumbling. Headaches, mild at first but increasingly severe, made their appearance four or five weeks before admission. They were not particularly localized to any one portion of his head.

Although the child had been normal in size and had possessed the usual physical and genital attributes of a 7 year old boy, the year before admission had witnessed an extraordinary change in these features. The parents believe that the transformation began at about the same time as his attacks of vomiting. He started to grow rapidly in height, and his genitals began to enlarge. At first little attention was paid to these phenomena since, his mother said, "he came of a large family." Soon a luxuriant growth of pubic hair appeared, and his voice changed

from a boyish soprano to a deep, husky baritone. His penis grew large and the parents became concerned at the repeated erections the boy was having. The mother watched him apprehensively for evidences of sexual interest in girls, but never witnessed any. He had never been observed to masturbate. The boy did not seem self-conscious with respect to these changes and continued to occupy himself with his usual playmates and toys. As evidence that there had been no alteration in mental and emotional attitudes, the mother emphasized that his constant playmate was a 5 year old neighbor child, with whom he continued to play as formerly, and that his favorite toys were small trains, wagons and auto-

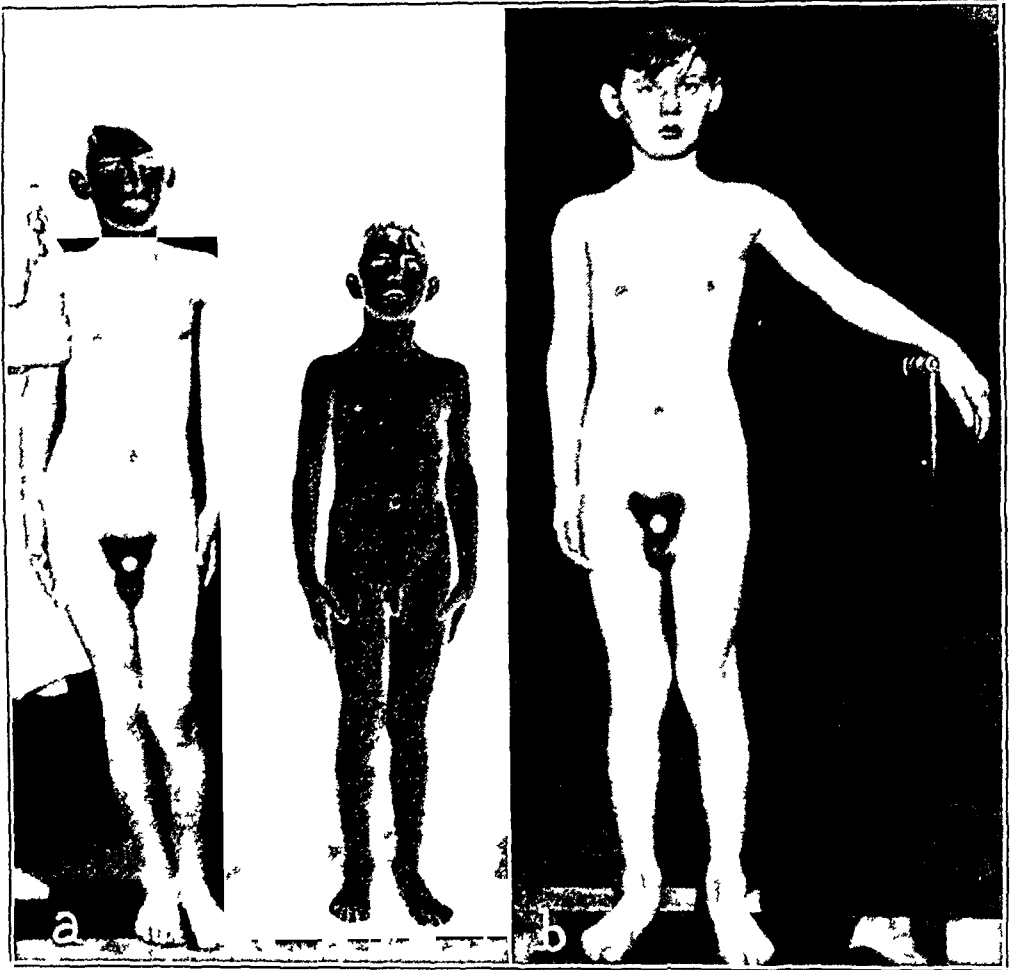


Fig 1—(a) The patient is shown beside a normal boy $7\frac{1}{2}$ years old. (b) The pubescent body contours are especially well demonstrated. The extremities are muscular, the feet large and strong and the genitals highly developed.

mobiles purchased at the ten cent store. His teacher had said nothing to the mother which would indicate any change in his behavior, other than to complain that the child was dull and inattentive in class. Despite rapid growth his appetite had been poor.

Physical Examination—The boy was 57.5 inches (146 cm) tall (normal 48.5 inches [123 cm]) and weighed 83 pounds (37.6 Kg). His size and unusual physical development can be appreciated from the photograph (fig 1a) taken beside a normal $7\frac{1}{2}$ year old boy. The circumference of the head was 55 cm, that of the chest 66 cm, that of the abdomen 63 cm, and that of the hips 79 cm.

His torso was long in comparison with his extremities. His body and extremities had lost their childish contours and were definitely adolescent in type. His hands and feet were large, he wore a $5\frac{1}{2}$ shoe—"men's size." His legs and arms were muscular, and, though his shoulders were broad, when viewed from behind he had rather feminine contours, his hips being wider than his shoulders. There was a dense growth of dark pubic hair, with a feminine escutcheon. There was no chest or axillary hair, but there was a fine dark mustache (fig 2*b*). His scalp had a thick growth of hair. The genitals were large, well formed and comparable in development with those of a man (fig 2*a*). The penis was 7.5 cm long and 3.75 cm wide at the base when flaccid. The testicles were the size of pecans, and the scrotum was pendant and darkly pigmented. The prostate gland and seminal vesicles were described by members of the department of



Fig 2—(a) The enlarged view of the genitals shows the large penis and the dependent, pigmented scrotum. The size of the testicles almost equals that of a man's. There is a thick growth of pubic hair, and the escutcheon is feminine in type. (b) Even in the strong light used in photographing, the pupils remain widely dilated. There is a dark mustache, only faintly shown. The facial features are more strongly formed than is usually seen at this age.

urology as "adult in character though proportional to the patient's size." Seminal fluid obtained by massage of the prostate gland was found filled with active spermatozoa, similar in number, morphologic character and motility to those occurring in the spermatic fluid of a normal man.

His voice was deep and baritone in pitch. The laryngeal cartilage was comparable with that of a young man. The larynx was examined by members of the department of laryngology, who reported "The larynx has the characteristics of an adult, the contour, thickness and length of the vocal cords compare favorably with those of an adult male."

He had 24 teeth, 12 on each jaw, and members of the dental department stated that this was a proper number for his age. They remarked that the only irregularity was the unusual largeness of his permanent teeth, the incisors and first molars being broader than the average.

His bone age, computed from roentgen examination of his hands, wrists, feet and pelvis, was reported as being slightly in advance of his chronologic age, perhaps comparable with that of a child of 9 or 10.

Neurologic Examination—His gait was ataxic, wide based and unsteady. There were static tremors of both upper extremities and, to a lesser degree, of the lower extremities. There were marked dyssynergia and dysmetria associated with impairment of the performance of rapid alternate movements. There was no definite loss of power in any of the extremities. The reflexes were hyperactive, but there were no pathologic ones. Sensation was everywhere intact. The pupils were widely dilated and reacted promptly in accommodation and convergence but responded feebly to light. Ocular rotations were full in all directions. There was a slight vertical nystagmus on upward gaze. There was bilateral papilledema of 4 D. Vision was reduced to 20/200 in each eye, but the peripheral visual fields were full to form. The cold caloric vestibular examinations, performed by members of the department of otology, gave results compatible with the presence of a midline supratentorial lesion, possibly involving the brain stem. This opinion was based on the elicitation of mixed and perverted nystagmus on stimulation of both sets of canals, together with the presence of bilateral spontaneous past pointing. Audiometric examination showed loss of hearing of 22 per cent in the right ear and of 28 per cent in the left ear. Roentgen examination of the skull revealed evidences of increased intracranial pressure, indicated by widening of the suture lines, increase in the convolutional markings and atrophy of the dorsum sellae.

Mental Status Psychologic and Psychometric Studies and Behavior—The child was studied in the psychologic laboratory and clinic of the University of Pennsylvania by Dr. Mildred Loring Sylvester, Dr. Katherine E. McBride, of Bryn Mawr College, also observed the child in the ward. Their findings are reported at some length because, except for a few instances in the literature, accurate testing of children with this condition has not been performed and there are many erroneous conceptions of their personalities and mental attributes.¹⁷

On the revised Stanford-Binet test the patient obtained a mental age of 6 years and 10 months, and an intelligence quotient of 86, which is definitely below normal. His memory spans were auditory-vocal forward 4 digits, auditory reverse 3 digits and visual 5 digits. These were considered below the average for his age. He was able to complete a 4 year old performance test using concrete material, although qualitatively the performance was poor and marked by poor discrimination and poor distribution of attention, however, some portion of his difficulty could be ascribed to muscular incoordination. He failed in a 6 year old test but was able to complete it on a second trial after being coached. His failures on the Stanford-Binet tests were largely in the field of memory. He was unable to pass all of the tests at the 7 year old level and passed only one test out of six at the 8 year

17 Doe-Kulmann, L., and Stone, C. P. Notes on the Mental Development of Children Exhibiting the Somatic Signs of Pubertas Praecox, *J. Abnorm. & Social Psychol.* **22**: 291, 1927. Keene, C. M., and Stone, C. P. Mental Status as Related to Pubertas Praecox, *Psychol. Bull.* **34**: 123, 1937. Gessell, A., Thoms, H., Hartman, F. B., and Thompson, H. Mental and Physical Growth in Pubertas Praecox. Report of Fifteen Years' Study of a Case, *Arch. Neurol. & Psychiat.* **41**: 755 (April) 1939.

old level. Members of the psychologic clinic classed him as dull normal, although they could not determine whether this represented deterioration due to his disease. For the latter reservation there was some basis, since a study of his classroom report cards showed that in the spring semester before admission he had received C in spelling, reading and arithmetic, while in the fall semester he had received D's in the corresponding subjects. Dr McBride found him friendly, spontaneous, cooperative and attentive, though showing some difficulty in concentrating. On the social maturity tests using the Vineland Scale the boy gave himself a rating of about 7 years, but conversations with his mother pointed to the fact that during his illness he had come to do less and less for himself. He was normally interested in childish material. On the whole, he seemed like the usual boy of 8, but somewhat more uncertain, anxious and quiet and less rather than more mature. He did seem to accept extensive psychologic testing better than the usual child, which possibly may be construed as a mark of maturity.

In the ward he lay quietly in bed and took little interest in ward activities. He occasionally laughed at the other children, but took no part in their conversation or play. He showed no interest in girl children or in the nurses. He was not observed to masturbate, nor did he show any evidence of sexual excitement while his legs and genitals were being washed. When questioned specifically concerning masturbation or sexual interest he denied both, although he seemed to have a clear understanding of what was asked him.

Special Tests and Observations—His basal metabolic rate, recorded on two occasions, was —29 and —30 per cent. Carefully kept records of his fluid intake and output showed persistently low values for both. His blood pressure varied between 98 systolic and 58 diastolic and 110 systolic and 70 diastolic. Temperature, pulse and respiratory rates were normal and agreed with one another. Blood studies showed red cells 4,400,000, hemoglobin concentration 85 per cent and white cells 6,400, with a normal differential count. The cholesterol content of the blood was 138 mg per hundred cubic centimeters, the calcium content 10.4 mg and the phosphorus content 5.2 mg. The fasting sugar content of his blood measured 60 and 68 mg per hundred cubic centimeters on two occasions, and the dextrose tolerance test showed a slightly delayed fall. The figures were 68 mg per hundred cubic centimeters during fasting, 145 mg at the end of one hour, 115 mg at the end of two hours and 96 mg at the end of three hours.

Endocrinologic Studies—Through Dr Charles Mazer and Dr S. Leon Israel, of Philadelphia, and Dr Ralph Dorfman, of Yale University, we were able to obtain complete endocrinologic studies.

On extraction of a twenty-four hour specimen of urine there was no demonstrable quantity of gonadotropic substance in as much as one sixth of the twenty-four hour specimen. The quantities of gonadotropin are not of especial importance, for Hamblen,¹⁸ among others,¹⁹ has pointed out that assays for gonadotropic substances are difficult to perform accurately and the results are unreliable. On two examinations with different seventy-two hour specimens, no demonstrable amount of active estrogen was found and only 3.0 to 3.8 rat units of inactive estrogens was demonstrated. These quantities were said by Dr Mazer to be no more than one would expect in a person on an average diet. There were three estimations of androgenic substances, McCullagh's chick technic being used. Three twenty-four hour specimens were obtained ten days apart. The first on analysis

¹⁸ Hamblen, E. C. *Endocrine Gynecology*, Springfield, Ill., Charles C Thomas, Publisher, 1939, p. 211.

¹⁹ Mazer, C., and Israel, S. L. Personal communication to the authors.

yielded 10 international units, from the second an assay was obtained of 45 international units, and from the third, 40 international units. Since it is well known that the amount of androgenic substance in the urine varies widely from day to day, we believe these quantities to be correct for the day on which they were assayed, especially since double check determinations were made.

Course—Under observation, the child gradually became duller and his neurologic disabilities increased. Operation seemed imperative. The clinical diagnosis was either pinealoma or teratoma of the pineal region with pubertas praecox. However, in view of the known intracranial conditions which may simulate both the neurologic and the somatic phenomena, notably hydrocephalus, a ventriculographic examination was thought to be warranted.

With the use of local anesthesia, both ventricles were tapped and found to be very large. In all, a total of 240 cc. of ventricular fluid was removed and replaced with an equal amount of air. Indigo carmine dye passed readily from one lateral ventricle to the other. Inspection of the roentgen films showed marked asymmetric

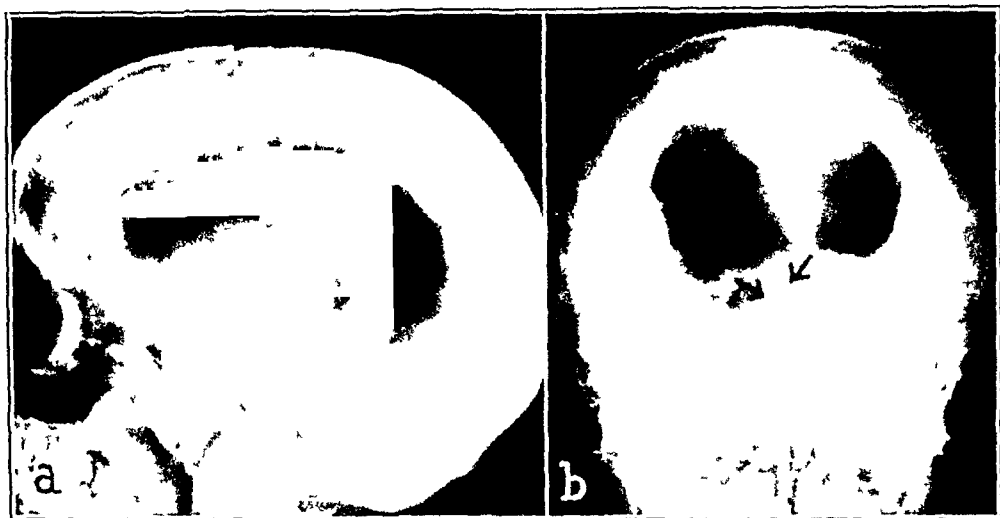


Fig 3—(a) The marked hydrocephalus is apparent. (b) The arrows indicate the superior margin of the tumor, which is outlined by a curved air shadow, probably representing the superior portion of a distorted third ventricle.

dilatation of the lateral ventricles. The third ventricle was not visualized except for a small amount of air in the anterosuperior portion, which outlined a mass apparently occupying the posterior and inferior portion of the ventricle (fig 3). These films were interpreted as revealing a large tumor involving the posterior portion and floor of the third ventricle and partially occluding the left foramen of Monro. It was also clear that the cerebrospinal outflow through the aqueduct was blocked.

Operation was performed December 8, twenty-four days after admission, with the boy under anesthesia induced by avertin with amylene hydrate supplemented by local anesthesia. A large right occipitoparietal cranioplastic flap was reflected (F C G). The bone flap was fashioned so that it crossed the midline for a short distance. The dura was opened from below upward until the longitudinal sinus was reached. The occipital lobe was then carefully retracted from the midline, and the veins crossing from the hemisphere to the longitudinal sinus were doubly clipped and cut. The calcarine vein, unfortunately, had to be sacrificed in order to free the occipital lobe from the falx. The lower margin of the falx cerebri containing the inferior sagittal sinus was clipped and cut and the falx slit

upward for several centimeters. The splenium of the corpus callosum thus exposed appeared thin and seemed to bulge upward. The splenium was split, and the tela choroidea containing the two lesser veins of Galen was visualized. The tela was incised between the two veins and the third ventricle opened. A large reddish tumor filled the third ventricle and was adherent to the under side of the galenic veins. At first glance it appeared to be encapsulated, but when dissection of the mass was commenced it was found to fade off into the lateral walls and floor of the third ventricle. During the attempt to isolate the mass from other structures, a small cyst contained within the tumor ruptured and spilled 2 or 3 cc of yellow fluid. The tumor appeared to be about 3 by 2 cm, although of course its true limits could not be seen. The larger amount of the gross tumor tissue was removed. The

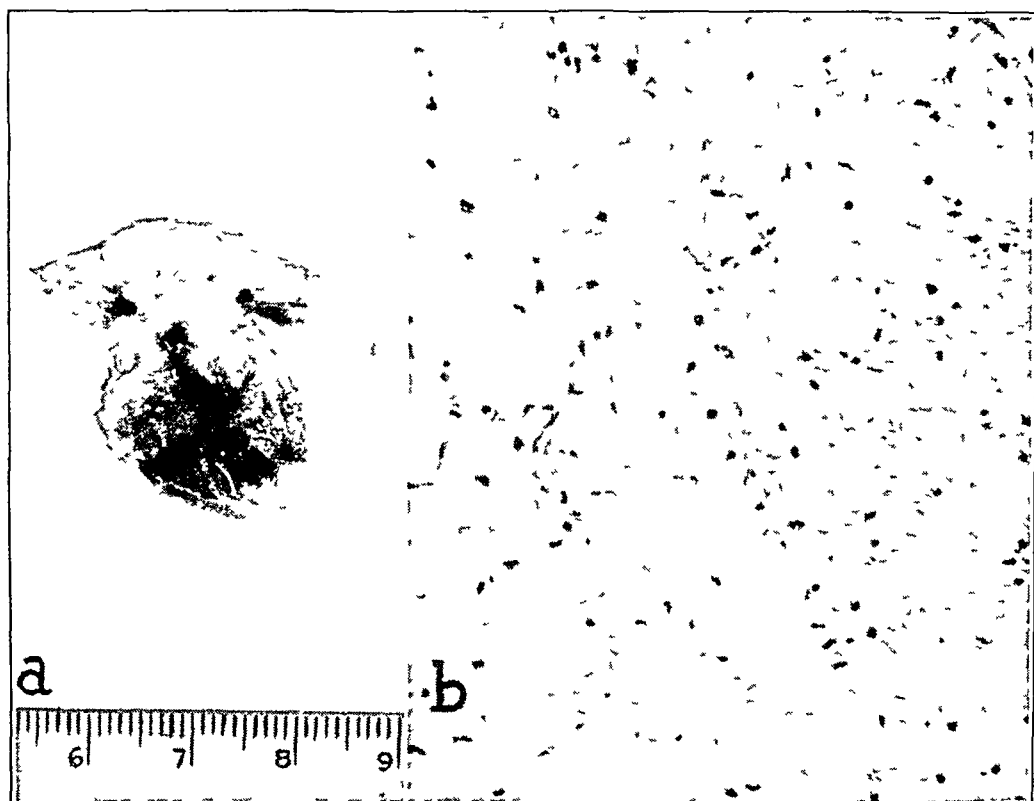


Fig 4—(a) The gross tumor. The ragged cavity at the inferior portion of the specimen marks the site of the ruptured cyst. (b) The tumor is thinly cellular and is apparently extremely slow growing. Cresyl violet stain $\times 200$.

pineal body was not seen, but the tumor was situated anterior and inferior to the habenular commissure and involved mainly the floor and the inferior portions of the lateral walls of the ventricle. After hemostasis was secured, the ventricular cavities were filled with warm Ringer's solution and the occipital lobe replaced. Owing to the venostatic edema, probably consequent to ligation of the large veins draining into the longitudinal sinus, the occipital lobe was so swollen that the bone flap had to be sacrificed. A firm closure of the dura was effected, however, by utilizing the pericranium.

Report of Microscopic Study—The portion of tumor removed weighed 6 Gm (fig 4a). The tissue appeared yellowish red after fixation. At one point was a small ragged cavity with brown walls which represented the ruptured cyst. On

microscopic examination, the tumor appeared unusual. It was composed of a thinly cellular tissue with no particular architecture or arrangement of the cells. The nuclei were round and contained fine chromatin granules. The greater part of the tumor was composed of loosely woven interlacing fibers. Gold and silver staining methods identified the cells and fibers as glial. The tumor was so poorly cellular that it appeared to be a malformation rather than true neoplasm (fig 4b). It was similar in most respects to the tumors described by Le Marquand and Russell^{19a} and by Gross^{19b} as hamartomas or malformations arising from the floor of the third ventricle.

Postoperative Course—The immediate postoperative course was stormy. Repeated ventricular taps were required to relieve intracranial pressure. The outstanding feature in the boy's immediate postoperative condition was the extreme rapidity of the pulse without a corresponding increase in the temperature. Blood lost during the operation had been adequately replaced by several transfusions. Aside from the rapidity, the pulse rate lost all relation to the temperature and went up or down independently of the temperature. In the first forty-eight hours the pulse rate varied between 120 and more than 200, although the temperature ranged only between 100 and 103 F. This curious phenomenon was interpreted as due to the release of uninhibited sympathetic mechanisms following manipulations in the floor of the third ventricle. Ten milligrams of acetylbetamethylcholine hydrochloride (mecholyl chloride) given intravenously reduced the heart rate to 8 within one minute, thus proving at least that the peripheral parasympathetic mechanisms were still responsive to parasympathomimetic stimulation. However, from the time of operation until discharge, two months later, the pulse rate remained out of proportion to the temperature and showed no correspondence with it.

The boy gradually improved and on the fourth day was conscious and fairly responsive. From this time progress was rapid, and by the end of two weeks he was up in a wheel chair. His behavior about this time is worthy of comment. Whereas before the operation he was tractable, quiet and customarily well behaved, afterward he became resistive and had violent temper tantrums whenever he was fed or bathed. He would strike the nurses, fight attempts to handle him and curse the nurses with obscene language. During this interval he was observed to masturbate frequently but ceased when reprimanded. When quizzed about his motives for such action, he admitted that it gave him pleasurable sensations and made him "feel better." No sexual fantasies could be elicited. He had, moreover, no sexual interest in his female attendants, or at least gave no evidence of it. The violent, impulsive, unrestrained behavior gradually quieted, and he returned after a few weeks to his preoperative state. After recovery from the operation he had left hemiplegia and left homonymous hemianopia. His pupillary reactions remained the same as previously. There was a static tremor of the right extremities, associated with marked incoordination. Intensive roentgen therapy was administered over a period of one month. A total of 5,550 r was given, of which 2,700 r was calculated as the effective tumor dose. There was considerable improvement in his neurologic status after roentgen treatment. At the time of discharge he was able to perform all but finger movements with his left hand, although there was still marked weakness. He was unable to walk, although he could stand when supported. The left homonymous hemianopia remained. Vision

19a Le Marquand, H. S., and Russell, D. S. A Case of Pubertas Praecox (Macrogenitosomia Praecox) in a Boy Associated with a Tumour in the Floor of the Third Ventricle, *Roy. Berkshire Hosp. Rep.*, 1934, p. 31.

19b Gross, R. E. Neoplasms Producing Endocrine Disturbances in Childhood, *Am. J. Dis. Child.* 59:579 (March) 1940.

was fairly good, he was able to read headlines and very large print. The papilloedema had disappeared, and there was early optic atrophy. The static tremors and incoordination of the right extremities showed no improvement. He was cooperative, cheerful and well behaved, although somewhat duller than on admission. His height on discharge was 60.25 inches (183 cm), which represented a growth of 2.7 inches (6 cm) in two and a half months. There had been no change in his secondary sexual characters.

COMMENT

Although there are many points of clinical interest that merit consideration, comment will be chiefly confined to the pathologic, physiologic and endocrinologic aspects of the case, especially those relevant to experimental knowledge concerning the integrations of the hypothalamo-hypophysoendocrine mechanisms.

The clinical features of our case did not emphasize the involvement of the hypothalamus. This is not particularly astonishing in light of the observation during the operation that the tumor largely involved the posterior segment of the hypothalamus. Such vegetative symptoms as somnolence, adiposity, diabetes insipidus and polyphagia, by which a hypothalamic tumor may be recognized, are largely referable to implication of the anterior portion of the hypothalamus. The patient in our case showed none of these symptoms. In fact, intake and excretion of fluid were inordinately low. The patient in a similar case reported by Gross also showed marked and persistent oliguria. As one glances over the table listing the collected cases one is struck by the fact that in only 5 were there symptoms commonly thought to be "hypothalamic," although there was in every case more or less damage to the floor of the third ventricle. The functions of the posterior portion of the hypothalamus are still obscure, although responses mimicking excitation of the sympathetic nervous system may be obtained by stimulation and the region appears to be concerned with the preservation of body heat. On the other hand, after an operation which entailed considerable manipulation within the third ventricle, there developed in our patient an unusually rapid pulse rate which was dissociated from the temperature, a phenomenon to which Strauss and Globus²⁰ have called attention as associated with hypothalamic tumors. Further, there developed in the child curious behavioral alterations, consisting of violent rages and unrestrained conduct, which have also been noted in cases of hypothalamic tumors by Alpers²¹ and others. Nevertheless, the boy did not show evidences of postoperative diabetes insipidus, adiposity or somnolence, which suggested that the anterior portion of the hypothalamus was not injured. The available observations indirectly point to predominant involvement

20 Strauss, I, and Globus, J. H. Tumor of Brain with Disturbance in Temperature Regulation, *Arch Neurol & Psychiat* **25** 506 (March) 1931.

21 Alpers, B. J. Relation of Hypothalamus to Disorders of Personality. Report of a Case, *Arch Neurol & Psychiat* **38** 291 (Aug) 1937.

of the posterior part of the hypothalamus. Our reasons for stressing this point and its relation to sexual precocity will be mentioned later. In this boy, all the physical attributes of puberty, if not of adulthood were present. Of particular interest was the presence of seminal fluid containing a full complement of motile spermatozoa. This indicates according to well established concepts, that the gonadotropic principle of the anterior lobe of the pituitary (the follicle-stimulating factor) was present in sufficient amounts to stimulate the spermatogenic cells of the testes to mature activity. What is even more significant is the proof of the activity of the testicular interstitial cells evidenced by the adult amounts of androgenic substance assayed in the urine. The interstitial cells, known to be responsible for the elaboration of the androgens which promote the secondary physical attributes of sexuality, are dependent for their stimulation and activation on the presence of the second principle from the anterior lobe of the pituitary, the luteinizing gonadotropic factor. Thus there is excellent indirect evidence that the anterior lobe of the hypophysis was releasing excessive quantities of the gonad-stimulating substances. Whereas the urine of the patient in our case contained as high as 45 international units of an androgen per twenty-four hour specimen, the normal excretion of androgen in an 8 year old boy is according to Nathanson, Towne and Aub,²² 60 to 99 international units daily.

REVIEW OF THE LITERATURE

Review of Pathologic Data on Hypothalamic Lesions and Precocious Puberty—At the onset the proposal was submitted that precocious puberty occurring with tumors of the brain, long thought to be connected with an alleged disturbance of the pineal body, is but a variant of hypothalamic sexual disturbances. This conception, suggested on clinical and pathologic grounds, was first voiced by Bailey and Bremer,²³ who wrote, apropos of pineal tumors and hypergenitalism: "The fact that these troubles [hypergenitalism] may be due to pressure on neighborhood centers is well shown by the constant occurrence of symptoms due to various lesions of the brain." Bing, Globus and Simon,^{15a} who recently collected and analyzed the cases in the literature, pointed out that in cases of pinealomas or teratomas of the pineal region the hypothalamus was invariably involved to some extent, usually a considerable one, and that in 70 per cent of the cases there were obvious symptoms of such involvement, namely, diabetes insipidus, polyphagia, adiposity, somnolence or disturbances in temperature. They also commented on the fact as others have, that pineal tumors may occur in children

22 Nathanson, I. T., Towne, L. E., and Aub, J. C. The Daily Excretion of Urinary Androgen in Normal Children, *Endocrinology* **24** 335, 1939.

23 Bailey, P., and Bremer, F. Experimental Diabetes Insipidus, *Arch. Int. Med.* **28** 773 (Dec.) 1921.

without causing pubertas praecox. Furthermore, there are many accounts in the literature of autopsies performed on children in whom the pineal body was found to be absent, atrophic, degenerated, calcified or destroyed by a cyst²⁴ but in whom there had been no evidence of precocious puberty. This array of negative evidence against the participation of the pineal body itself in the syndrome of pubertas praecox, while strongly suggestive, is not conclusive. More important, and certainly more convincing, are those cases of precocious puberty associated with various lesions in the hypothalamus and the third ventricle in which the pineal body was unaffected. Precocious puberty has been observed in association with hydrocephalus in which the third ventricle was subjected to marked distention from aqueductal block,²⁵ following encephalitis lethargica,²⁶ in which the main site of inflammation is in the diencephalon, and following tuberculous²⁷ or syphilitic meningoencephalomyelitis. In cases of the last condition histologic studies demonstrated proliferating ependymitis of the floor and walls of the third ventricle. It has also been reported in connection with a heterogeneous group of cerebral diseases, such as postmeasles encephalomyelitis,²⁸ degenerative encephalopathies²⁹ and nonspecific inflammations of the

24 Laignel-Lavastine, M. *Anatomie pathologique de la glande pineale*, *Encephale* **16** 225, 1921. Lord, J. R. *The Pineal Gland Its Normal Structure, Some Remarks on Its Pathology, a Case of Syphilitic Enlargement*, *Tr. Path. Soc. London* **50** 18, 1899. Krabbe⁴. Schnepf and Marburg, cited by Ewing, J. *Neoplastic Diseases*, ed. 2, Philadelphia, W. B. Saunders Company, 1922. Scheerer, G. *Enlargement of the Pineal Gland and Sclerosis of the Brain*, *Edinburgh M. J.* **21** 297, 1875.

25 (a) Neale, A. V. *Precocious Puberty with a Report on a Case of Pineal Syndrome*, *Arch. Dis. Childhood* **13** 241, 1938. (b) Egas Moniz and Almeida Lima. *Paraplegie et macrogenitosomie precoce dans un cas d'hydrocephalie congenitale avec os du crâne épais*, *Rev. neurol.* **1** 693, 1932. (c) van der Scheer, W. M. *Clinical Syndromes of the Pituitary Hypothalamic Connections*, *Psychiat. en neurol. bl.* **6** 753, 1939.

26 (a) Wimmer, A. *Chronic Epidemic Encephalitis*, London, W. Heinemann, 1924, p. 82, case 14. (b) Cited by van der Scheer^{25c}. (c) Stern, cited by Wimmer^{26a}. (d) Lhermitte, J. *Macrogenitosomie precoce, hallucinations et narcolepsie dans un cas d'encephalite epidemique*, *Rev. neurol.* **1** 65, 1938.

27 Poos, F. *Ueber eine seltene, chronische Verlaufsform tuberculoer Meningo-Encephalitis im Kindesalter mit Pubertas praecox, Stauungspapille und bitemporaler Hemianopsie*, *Klin. Monatsbl. f. Augenh.* **95** 537, 1935.

28 Ford, F. R., and Guild, H. *Precocious Puberty Following Measles Encephalo-Myelitis and Epidemic Encephalitis*, *Bull. Johns Hopkins Hosp.* **60** 192, 1937.

29 Fiszhaut-Zeldowicz, L. *Macrogenitosomie precoce chez un enfant atteint d'encephalopathie chronique diffuse*, *Rev. neurol.* **72** 188, 1939. Lhermitte, J. *Macrogenitosomie precoce*, *ibid.* **69** 380, 1938. Cornil, L., and Kissel, P. *Macrogenitosomie precoce. Arriération mongoloïde. Adénomes sébacés du visage*, *ibid.* **1** 86, 1930.

brain.³⁰ While autopsy protocols are largely wanting in cases of the last group, the patients in a number of the cases presented symptoms referable to injury of the hypothalamic vegetative mechanisms.

Far more significant for our purposes is the small group of cases of tumors which have mainly or wholly implicated the hypothalamus, spared the pineal body and yet produced precocious puberty. We have been able to cull 15 such cases from the literature, in addition to our own.³¹ It is particularly these to which we shall direct attention, because they form the first substantial link in the chain of evidence pointing to precocious puberty as a hypothalamic syndrome. In scanning the table, in which are listed the salient features of the collected cases, one is struck by the fairly sharp localization of most of the tumors. Except in the 4 cases of suprasellar tumor, the neoplasms predominantly involved the posterior portion of the floor of the third ventricle. Repeatedly the mamillary bodies were described as involved or destroyed. In the cases of Heuyer, Lhermitte, de Martel and Vogt,^{31c} in the case reported by Le Marquand and Russell³¹ⁱ and in that described by Krabbe,^{31a} the tumors were so small and so restricted to the mamillary bodies that they may almost be compared to experimental lesions. Driggs and Spatze^{31m} reported an exceptionally well studied case in which a small tumorous malformation, the size of a cherry stone, hung from the floor of the third ventricle between the mamillary bodies and the tuber cinereum. In the cases of Dew,^{31f} Vickers and Tidswell^{31g} and Wieland,^{31c} the tuber cinereum and the infundibulum were involved in

30 Schlesinger, B. Hydrocephalus with Precocious Puberty Following Post-Basic Meningitis, *Proc Roy Soc Med* **28** 149, 1934.

31 (a) Krabbe, K. H. La sclerose tubereuse du cerveau et l'hydrocephalie dans leurs relations avec la puberte precoce, *Encephale* **17** 281, 1922. (b) Schmalz, A. Ueber einen Fall von Hirntumor mit Pubertas praecox, *Beitr z path Anat u z allg Path* **73** 168, 1925. (c) Wieland, E. Macrogenitosomia Praecox bei 4½-jährigen Knaben mit Carcinom des dritten Hirnventrikels und intakter Zirbeldrüse, *Praxis* (pt 2) **17** 9, 1928. (d) Horrax, G., and Bailey, P. Pineal Pathology [case 3], *Arch Neurol & Psychiat* **19** 394 (March) 1928. (e) Heuyer, G., Lhermitte, J., de Martel, J., and Vogt, C. Un cas de macrogenitosomie précoce liée à un ependymogliome de la region mamillo-tubérale, *Rev neurol* **2** 194, 1931. (f) Dew, H. R. The Simulation of Pituitary Disease by Intracranial Lesions, *M J Australia* **2** 771, 1932. (g) Vickers, W., and Tidswell, F. A Tumor of the Hypothalamus, *ibid* **2** 116, 1932. (h) Frazier, C. H. Lesions in and Adjacent to the Sella Turcica [case 8], *Am J Surg* **16** 199, 1932. (i) Le Marquand and Russell^{19a}. (j) Saar, H. Pubertas praecox bei Gliom des Zwischenhirnes. Ein Beitrag zur Frage der innersekretorischen Funktion der Zirbeldrüse, *Frankfurt Ztschr f Path* **50** 451, 1937. (k) Ford, F. R. Diseases of the Central Nervous System in Infancy, Childhood and Adolescence, Springfield, Ill., Charles C Thomas, Publisher, 1937, p. 687. (l) Bailey, P., Buchanan, D. N., and Bucy, P. C. Intracranial Tumors of Infancy and Childhood, Chicago, University of Chicago Press, 1939, cases 68 and 91. (m) Driggs, M., and Spatze, H. Pubertas Praecox bei einer hyperplastischen Missbildung der Tuber cinereum, *Virchows Arch f path Anat* **305** 567, 1939. (n) Gross^{10b}.

Summary of Data on Sixteen Cases of Hypothalamic Tumor Associated with Precocious Puberty

Case	Author, Date	Age, Yr, Sex	Symptoms and Signs	Pathologic Findings	Status of Pinea Body	Status of the Other Endocrine Organs	Symptoms and Signs Referred to Hypothalamus
1	Krabbe 1922	4 M	Genitals enlarged early in life, erections at 1 yr height 72 cm, weight 80 Kg, penis 7 cm long, testicles large pubic hair and mustache mental retardation	Egg sized nodule of tuberculous sclerosis between infundibulum and mamillary bodies, with latter mainly involved, internal hydrocephalus	Normal	Weight of testes 7 and 6 Gm, active spermatogenesis, pancreas and thyroid, adrenal and prostate glands normal	None
2	Schmalz 1925	9 M	Large genitals, pubic and axillary hair and mustache height 136 cm weight 35 Kg	Cellular neurofibroma of floor of third ventricle encroaching on basal ganglions	Normal	Spermatogenesis and mature sperm in testes, pituitary, adrenal and thyroid glands normal	None
3	Wieland 1928	1 M	Genitals enlarged penis 10 cm long when flaccid, frequent erections, pubic hair and mustache deep voice, no sexual interest and behavior childish height 109 cm, I Q of child of 2 yr, emaciation	Carcinoma (?) arising from region of infundibulum	Normal	?	Diabetes insipidus emication
4	Horrax and Bailey 1928	7 M	Genitals enlarged, pubic and axillary hair at age of 3 voice changed at age of 4, height 140 cm, weight 50 Kg, bone age 18 adult configuration of body	Ginghioneuroma of floor of third ventricle attached to infundibular region	Normal	Sperm and adult interstitial cells in testes thyroid, thymus, adrenal and pituitary glands normal	Adiposity, diabetes insipidus
5	Heuyer, I hermitte, de Martel and Vogt 1931	6 M	Precocious development at 4 yr, appearance of 13 year old child, large genitals, pubic hair, deep voice, height 129 cm, weight 30 Kg mental age 3	Small hard ependymoma mainly involving mamillary bodies infiltrated tuber infundibulum	Normal	Testes and adrenal glands grossly normal	None
6	Dew 1932	8 M	Large genitals and pubic hair at 3½, axillary hair at 4 mustache and deep voice at 6, seminal emissions, muscular extremities, imitation of adults, but mental retardation	Astrocytoma of floor of third ventricle, obliterating mamillary bodies and tuber cinereum	Normal	Pituitary and all other endocrine glands normal	Violent rages psychomotor fits
7	Vickers and Tidswell 1932	8 M	Full hirsuties at age of 3 and rapid enlargement of genitals from birth voice deep, seminal emissions, no later growth disturbances	Walnut sized astrocytoma in floor of third ventricle mamillary bodies and tuber cinereum destroyed	Normal	Testes and pituitary thyroid and adrenal glands normal	Periodic temperatures and outbursts of rage no disturbances of water or carbohydrate metabolism

			Suprasellar teratoma	?	?	None
8	Frazier 1932	15 M	Developed sexual precocity at age of 10 to 11, large penis, pubic hair, deep voice, nocturnal emissions, interest in female sex such that mother wanted boy castrated			
9	LeMarquand and Russell 1934	4½ M	Precocious puberty, hypergenitalism and hirsuties, attacks on women, great obesity and size, tremendous strength	Normal	Spermatozoia and conspicuous interstitial cells in testes, pituitary, adrenal and thymus glands and pancreas normal	Consistently low body temperature, mammary hyperactivity
10	Sair 1936	9 M	Hypergenitalism at age of 1, masturbation at age of 1 to 8, adult genitals and pubic hair, senile faces, penis 7 cm long, testicles large, mustache present, height 135 cm	Normal	Testes normal, spermatozoia but no sperm, pituitary, thyroid and adrenal glands normal	None
11	Ford 1937	12 M	Rapid enlargement of genitals at age of 10, adult development of genitals, pubic hair thick, attempts to pinch nurses	?	?	Enormous appetite and obesity
12	Biley, Buehman and Buey 1939	9½ M	Older than years, pubic hair and abnormal secondary sexual development	Normal	?	?
13	Bailey, Buchanan and Buey 1939	9 F	Breasts enlarged at age of 7, pubic hair at age of 8, no menstruation, mature figure, large breasts, thick pubic hair	?	?	Urinary output 900 to 1,500 cc, basal metabolic rate -15 to -25 per cent
14	Driggs and Spittler 1939	1½ M	Large genitals, pubic hair and erections at age of 2, deep voice, mustache, normal mental condition, bone age 13, height 115 cm, extraordinary muscular development, testes large	Normal	Overgrowth of interstitial cells but little adult sperm in testes, predominance of eosinophilic cells in pituitary body, adrenal and thymus glands and pancreas normal	None
15	Gross 1940	2 F	Breasts enlarged at 19 mo., with onset of menstruation, vulval and pubic hair at 24 mo., great obesity, pigmented areoles, height 95 cm, estrogen excretion of a woman, normal intelligence	Normal	Pituitary and adrenal glands normal, mature graafian follicles in ovaries, endometrial tissues hyperplastic	Obesity, oliguria
16	Weinberger and Grant 1940	8 M	Rapid enlargement of genitals at 7, pubic hair, deep voice, rapid increase in height, penis 7.5 cm long, adult seminal fluid, testes large, height 144 cm, mental retardation and childish behavior, androgen excretion of man	?	Active spermatogenesis	Basal metabolic rate -30

* The sign "?" indicates that no mention was made

addition to the mamillary bodies, although the latter in each instance were spoken of as destroyed or obliterated. In 12 of the 15 cases the pineal body was specifically reported as normal. In 3 cases, while no information was given, the nature of the tumor (suprasellar craniopharyngioma and teratoma) largely precluded the likelihood of the pineal body being involved. In our own case we cannot be positive on this point, but our findings during the operation led us to believe that the tumor was situated anterior and inferior to the pineal body. Buescher³² was the first to call attention to the relation of the region of the mamillary bodies to sexual function. Heuyer, Lhermitte, de Martel and Vogt^{31e} also suggested on pathologic grounds that lesions of the mamillary bodies might be significant in the production of precocious puberty, although their hypothetic pathophysiologic explanation was not convincing. While the exact structures, pathways or mechanisms involved are still unknown, a summary of the pathologic evidence as obtained from the study of hypothalamic tumors, points to the posterior portion of the hypothalamus as the critical area involved in the production of precocious hypersexuality. It seems more than coincidental that pinealomas or teratomas of the pineal region impinge on or first infiltrate precisely this area. Teratomas of the pineal region are more commonly associated with *pubertas praecox* than are primary pineal tumors.³³ Teratomas which exist from birth have the advantage of time in producing their pathologic effects on the hypothalamus and, moreover, exert these effects while the person is young. The tumors of the posterior region should be contrasted with those of the anterior portion of the hypothalamus, which result in sexual dystrophy and hyposexuality.

The physiologic explanation, however, of hypergenitalism, as well as of hypogenitalism, associated with hypothalamic lesions has awaited researches in experimental neuroendocrinology. Though the literature is rich in pathologic and experimental observations on the sexual changes following destructive lesions in the hypothalamus,³⁴ less is known concerning the locus of the neurosexual mechanisms and their mode of action in the intact or nearly intact organism. Recent experimental work, however, has thrown considerable light on these matters. We feel that it is now possible to assemble sufficient data to offer a reason-

32 Buescher, J, in Muller, L R. *Die Pathologie der Nervenversorgung der Sexual Organe. Die Lebensnerven*, Berlin, Julius Springer, 1924, p. 338.

33 Bochner, S J, and Scarff, J E. *Teratoma of the Pineal Body. Classification of the Embryonal Tumors of the Pineal Body, Report of a Case of Teratoma of the Pineal Body Presenting Formed Teeth*, Arch Surg **36** 303 (Feb) 1938.

34 (a) Cushing, H. *Pituitary Body, Hypothalamus and Parasympathetic Nervous System*, Springfield, Ill, Charles C Thomas, Publisher, 1932. (b) Camus, J, and Roussy, G. *Polyurie experimentale permanente (diabete insipide)*, Compt rend Soc de biol **83** 764, 1920. (c) Aschner, B. *Ueber die Funktion der Hypophyse*, Arch f d ges Physiol **146** 122, 1912.

able physiologic explanation for and to elucidate the pathogenesis of precocious puberty accompanying a hypothalamic tumor, as well as to explain by analogy the phenomenon when it occurs with other conditions affecting this region. This involves consideration of the physiologic evidence linking the hypothalamus with the pituitary body and the pituitary body in turn with the gonads, secretion of potent hormonal substances from which ultimately produces the secondary sexual characters.

Review of Data Concerning the Role of the Hypophysis in Precocious Puberty and Its Association with Gonadal Functions—It was stated earlier that while precocious puberty has never with certainty been produced by manipulations of the pineal body or injections of its extracts, it has for many years been produced with extracts of the anterior lobe of the pituitary gland. Smith³⁵ made the observation a number of years ago that daily homoplastic transplants of the pituitary gland from adult rats into immature female rats caused sexual precocity, the rats reaching sexual maturity in half the expected time. A short time later Smith³⁶ was able to prove that transplantation of the anterior lobe only was essential. These fundamental discoveries have since been confirmed by many workers and form the starting point of modern endocrinologic knowledge. In 1928 Aschheim and Zondek³⁷ found that the anterior lobe of the pituitary gland in the female animal contained two hormonal fractions, one of which (the follicle-stimulating factor) caused the ripening of the ovarian follicle and the other (the luteinizing factor) resulted in the formation of the corpus luteum. To make a long story short, it is now known that the same two fractions exist in the pituitary gland of the male animal, the follicle-stimulating factor promoting the process of spermatogenesis and the luteinizing factor activating the interstitial cells of the testes. In males, as in females, injections of extracts from the anterior lobe of the pituitary body into immature animals causes swift development of the sexual accessories, accompanied by hypertrophy of the interstitial testicular cells³⁸. The ovaries of the females and the interstitial cells of the males in turn elaborate the estrogenic and androgenic substances, respectively, which promote the

35 Smith, P. E., and Engle, E. F. Experimental Evidence Regarding the Role of the Anterior Pituitary in the Development and Regulation of the Genital System, *Am J Anat* **40** 159, 1927.

36 Smith, P. E. The Induction of Sexual Precocity by Pituitary Homeo-Transplants, *Am J Physiol* **80** 114, 1927.

37 Aschheim, S., and Zondek, B. Schwangerschaftsdiagnose aus dem Harn (durch Hormonnachweis), *Klin Wchnschr* **7** 8, 1928. Zondek, B. Das Stellung des weiblichen Sexualhormons aus dem Harn, insbesondere dem Harn von Schwangeren, *ibid* **7** 485, 1928.

38 Greep, R. O. Pituitary Regulation of the Male Gonad, in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1937, vol. 5, p. 136.

development of the secondary sexual characters, as well as general somatic growth. Thus it comes to pass that normal sexual maturity results primarily from the secretion of the hypophysial gonadotropic substances and, further, that sexual maturity may be hastened by the forced administration of these substances. Moore³⁹ has pointed out that in the male, also, the testes may respond to the stimulation by forced administration of anterior pituitary extracts long before the phases of maturity of the organism would normally bring them into activity. This brief review of the pituitary-gonadal physiology, so easy in the telling, though requiring years of labor to elucidate, explains the effect on human beings, particularly the male, of large doses of gonadotropic substances from the anterior lobe. In 1938 Thompson and Heckel⁴⁰ reported that during the treatment of undescended testicles by the repeated administration of anterior-pituitary-like principles obtained from the urine of pregnant women, in more than half of the young boys thus treated evidences of precocious puberty developed. In the cases of 2 boys this was striking, in both of the boys, 6 and 9 years old, respectively, large genitals developed, a heavy growth of pubic hair appeared and a decided increase in weight and height occurred. Their voices changed, they had frequent penile erections, and they began to masturbate. This remarkable result demonstrates with all the precision of a laboratory experiment the effect of anterior pituitary hormones on sexual and somatic development in the human being. In man one can estimate the function of the anterior lobe of the pituitary body indirectly by quantitative determinations of the androgenic or estrogenic substances in the urine. It is not practicable, at present, to determine it directly by assays of the gonadotropic substances in the urine of normal males or non-pregnant females.¹⁸

It has been frequently commented on that tumors of the pituitary body have never been observed in cases of precocious puberty. This observation is undoubtedly true with respect to the chromophobic adenomas, in which the active cells of the anterior lobe are compressed and destroyed by the hyperplasia of the inactive chromophobic elements. On the other hand, a marked intensification of libido and virility, as well as an overdevelopment of the sexual characteristics, has been noted early in the course of acromegaly. These changes, observed by Cushing,⁴¹ Cushing

39 Moore, C. R. Testes Hormone Secretion and Some Effects of the Hormone in the Organism, in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1937, vol. 5, p. 115.

40 Thompson, W. O., and Heckel, N. J. Precocious Sexual Development from an Anterior Pituitary-Like Principle, *J. A. M. A.* **110** 1813 (May 28) 1938.

41 Cushing, H. The Pituitary Body and Its Disorders, Philadelphia, J. B. Lippincott Company, 1912.

and Davidoff⁴² and Severinghaus,⁴³ have been correlated with an increase in the gonad-stimulating substances in the urine, presumably due to the hyperplasia of the eosinophilic cells. The eosinophilic cells, it is generally suspected, are responsible for the gonadotropic substances.⁴³ One may mention still another line of evidence that bears directly on the hypothalamohypophyseal hormonal relationships. There are rare cases in which acromegaly has occurred without the presence of an eosinophilic adenoma. Cases of such a condition, probably dependent on overfunctioning of the normal complement of eosinophilic cells, although hyperplasia occurs in some instances, have been observed after encephalitis lethargica⁴⁴ or after the development of hydrocephalus.⁴⁵ There is ample reason to think that in both these pathologic conditions the walls and the floor of the third ventricle have been injured. In this connection it is interesting to cite the work of Kraus,⁴⁶ who investigated the effect of increased intracranial pressure on the endocrine system. He found that when there was no destruction of the hypothalamus, hypophysis or infundibulum, although the walls of the third ventricle might be thinned from pressure, the pituitary glands when assayed biologically by their effect on immature mice showed a 60 per cent increase of the follicle-stimulating factor in females. The Aschheim-Zondek test gave a positive reaction of 1 plus to 3 plus. Several males showed an increase in the follicle-stimulating factor. Henderson and Rowlands,⁴⁷ who repeated this work in part, could not verify it, although they expressed the opinion that the hormonal content of such pituitary glands was more variable than normal.

42 Cushing, H., and Davidoff, L. M. The Pathological Findings in Four Autopsied Cases of Acromegaly with a Discussion of Their Significance, Monograph 22, Rockefeller Institute for Medical Research, 1927, p. 121.

43 Severinghaus, A. E. Cellular Changes in the Anterior Hypophysis with Special Reference to Its Secretory Activities, *Physiol Rev* **17** 556, 1937.

44 Bremer, cited by Bailey, P. Die Funktion der Hypophysis cerebri, *Ergebn d Physiol* **20**.163, 1922. Gans and Erdheim, cited by van der Scheer^{25c}. Aschner^{34c}.

45 Pollak, F. Zur Frage der cerebralen Trophik. Klinische Erfahrungen bei Morbus Reynaud, einseitigem Überwachstum der Extremitätenenden (O. Fisher), systemisierter Hemiatrophie und Hemihypertrophie, *Arch f Psychiat* **89** 788, 1930. Sacchetti, N. Funzione del diencefalo e sviluppo dell'acromegalia, *Riv di pat nerv* **44** 433, 1934. Rosenstein. Acromegalia sans tumeur de l'hypophyse, Thesis, Paris, 1929, cited by van der Scheer^{25c}.

46 Kraus, E. J. Hypophyse und Ovarien bei chronischem Hirndruck, *Med Klin* **27** 547, 1931, Ueber Veränderungen der Hypophyse bei chronischem Hirndruck, *Ztschr f d ges Neurol u Psychiat* **146** 548, 1933.

47 Henderson, W. R., and Rowlands, I. W. The Gonadotropic Activity of the Anterior Pituitary Gland in Relation to Increased Intracranial Pressure, *Brit M J* **1** 1094, 1938.

All these data suggest that hypothalamic lesions under certain circumstances may excite the anterior lobe of the pituitary gland to release abnormally large amounts of gonadotropic substances, which ultimately, through the intermediation of the gonads, result in premature growth of the secondary sexual characters. Proof of this final result, if not of the primary stimulus, should be expected in an increased excretion of estrogenic or androgenic substances in cases of precocious puberty due to hypothalamic tumors. Besides the report of our own case, in which the excretion of androgen attained an adult level and thus fulfilled the expectation, there are two other valuable studies in the literature. In Gross's³¹ case of a 26 month old girl with marked precocious puberty due to a verified tumor in the posterior portion of the floor of the third ventricle, estrogenic assays on successive days yielded the following results: 405, 324, 648, 36, 175, 270 and 12 international units. The normal woman excretes between 50 and 600 international units daily, so that in this case the excreted quantities were comparable with those of a woman. Horrax⁴⁸ reported a case of *pubertas praecox* in a 10 year old boy who showed high development of the sexual attributes. The diagnosis was not histologically verified, but the ventriculographic study demonstrated a large mass in the posterior portion of the third ventricle. Ten cubic centimeters of the boy's urine injected into a capon produced growth of the comb, spurs and tail plumes. This result from such a small amount of urine indicates a large excretion of androgen.

Further studies along this line are urgently needed. If one may be permitted, however, to draw any conclusions from so few data, the evidence suggests that precocious puberty results primarily from an increased functioning of the hypophysis and that, further, this hyperfunction may be produced pathologically early in life by hypothalamic influences mediated through the anterior lobe of the pituitary gland. Following this line of reasoning, we are brought to a consideration of the hypothalamohypophysial relationships as regards normal sexual function.

Review of the Data Concerning the Regulation of the Hypothalamohypophysial Sexual Mechanisms—Though many clinical and experimental observations attest to the effects of destructive lesions on the hypothalamus with respect to sexual function, little has been known until recently concerning the approximate localization of the integrating mechanisms and their mode of functioning. Current research has attacked the problem along two lines: (1) the determination of the locus of the sexual integrating mechanisms in the hypothalamus and

48 Horrax, G. Further Observations on Tumor of the Pineal Body [case 2], *Arch Neurol & Psychiat* **35** 215 (Feb.) 1936

(2) the functional and neural connections between the hypothalamus and the hypophysis which mediate sexual influences

The localization of the sexual centers in the hypothalamus has been pursued with both ablation and stimulation technics. Marshall and Verney⁴⁹ showed that stimulation of the brain stems of female rabbits produced ovulation and the changes of pseudopregnancy. Haterius and Derbyshire,⁵⁰ attempting to localize this response more accurately, were able to produce ovulation in the rabbit by direct electric stimulation of the hypothalamus, obtaining the positive responses largely from the anterior portion of the hypothalamus. Harris,⁵¹ using a different type of current, obtained the same results but was also able to cause ovulation by stimulation of the posterior portion of the hypothalamus just rostral to the red nucleus. Recently Benoit and Kehl⁵² reported interesting experiments in which they produced rapid testicular growth in drakes by the direct application of light to the hypothalamus. Other investigators have attacked the same problem somewhat indirectly by attempting to localize the mechanisms responsible for the integration of the motor patterns of mating and estral behavior. Bard⁵³ found that estral mating behavior patterns in the cat survived complete decortication. In further experiments, Dempsey and Rioch⁵⁴ found that estral behavior survived transections of the brain stem as long as the transections were made anterior to the mamillary bodies. Sections posterior to these structures abolished estral behavior. They concluded that the essential part of the mechanism integrating mating behavior is located between the anterior margins of the mamillary bodies and rostral to the intercollicular level. In pointing out the sites of the tumors accompanied by *pubertas praecox*, we have called attention to the repeated implication of the region of the mamillary bodies in reported cases. In view of the experimental work just cited, this association acquires an added significance. However, in the cases in man it was this region that was injured. While this may seem to be contradictory evidence, actually such is not the case.

49 Marshall, F. H. A., and Verney, E. B. The Occurrence of Ovulation and Pseudo-Pregnancy in the Rabbit as a Result of Central Nervous Stimulation, *J Physiol* **86** 327, 1936.

50 Haterius, H. O., and Derbyshire, A. J. Ovulation in the Rabbit Following upon Stimulation of the Hypothalamus, *Am J Physiol* **119** 329, 1937.

51 Harris, G. W. The Induction of Ovulation in the Rabbit by Electrical Stimulation of the Hypothalamic-Hypophysial Mechanism, *Proc Roy Soc., London, s B* **122** 374, 1937.

52 Benoit, J., and Kehl, R. Nouvelles recherches sur les voies nerveuses photoreceptrices et hypophysostimulantes chez le canard domestique, *Compt rend Soc de biol* **131** 89, 1939.

53 Bard, P. Oestral Behavior in Surviving Decorticate Cats, *Am J Physiol* **116** 4, 1936.

54 Dempsey, E. W., and Rioch, D. M. Localization in the Brain Stem of Oestrous Response of Female Guinea Pigs, *J Neurophysiol* **2** 9, 1939.

It is improbable that such a highly complicated mechanism can be explained in simple terms of ablation. If, as we suspect, this region is actively concerned with the production of precocious puberty, the phenomenon may result from the destruction of some tract or the inhibition of some mechanism which ordinarily checks the rate or intensity of impulses passing to the pituitary gland. This appears more logical and more in keeping with accepted conceptions of "release phenomena" than to imagine that a destructive lesion causes stimulation through irritation.

Further indication of the importance of this general area in relation to sexual activities is the observations of Brooks⁵⁵. He found that while mating activity in the rabbit survived complete decortication, it was abolished by decortication plus removal of the olfactory bulbs. This suggests that mating depends in some way on or is in part a function of olfaction. One has only to recall in this connection that the mamillary bodies are important centers in the olfactory pathways.

The functional and neural relations of the hypothalamus to the posterior lobe of the pituitary gland are now a matter of common knowledge. Less clear at present are those between the hypothalamus and the anterior lobe of the pituitary, though there can hardly be any doubt of their presence. Endocrinologic research is gradually accumulating information of the relations between these two structures with regard to sexual functions. A number of years ago Fee and Parkes⁵⁶ discovered that rabbits, a species which requires copulation in order to ovulate, did not ovulate if hypophysectomized and decerebrated within an hour after copulation. If decerebration was delayed for more than an hour, ovulation went on to completion. This indicates that the act of mating sets into action emotional excitatory impulses which in some way cause release of gonad-stimulating substances from the anterior lobe of the pituitary gland. These, as Cushing⁵⁷ pointed out, could scarcely be discharged except through the intermediation of the diencephalon. Since then experiments have been designed to show the influence of the hypothalamus in either initiating or relaying impulses to the cells releasing gonadotropic substances from the anterior lobe of the pituitary gland. Westman and Jacobson⁵⁸ found that ovulation experimentally

55 Brooks, C. M. The Role of the Cerebral Cortex and of Various Sense Organs in the Excitation and Execution of Mating Activity in the Rabbit, *Am J Physiol* **120** 544, 1937.

56 Fee, A. R., and Parkes, G. S. Studies on Ovulation. Relation of the Anterior Pituitary Body to Ovulation in Rabbit, *J Physiol* **67** 383, 1929.

57 Cushing,^{34a} p. 43.

58 Westman, A., and Jacobson, D. Experimentelle Untersuchungen über die Bedeutung des Hypophysen-Zwischenhirnsystems für die Produktion gonadotroper Hormone des Hypophysenvorderlappens, *Acta obst et gynec Scandinau* **17** 235, 1937.

produced by electrical stimulation of the brain could be abolished by transection of the hypophysial stalk if performed within an hour after stimulation. They concluded that the failure of ovulation was due to interruption of central impulses normally passing through the hypophysial stalk. Brooks⁵⁹ investigated this functional connection with great care and found that female rabbits permanently failed to ovulate or to become pregnant, though they repeatedly mated, after transection of the pituitary stalk. Haterius,⁶⁰ reviewing the evidence bearing on the cause of this behavior, showed that such stalk-transected animals remained in constant estrus, however, ovulation did not occur because the luteinizing factor was absent in these isolated pituitary glands. He concluded that loss of the neural control prevents release of the luteinizing factor. Ingram,⁶¹ on the other hand, found that cats in which the hypothalamohypophysial connections had been injured did not enter into estrus. Brooks and Lambert⁶² also stated in a later paper that the amount of gonadotropic substances in the pituitary glands of stalk-cut female rabbits was normal. The failure of the ovulatory mechanism thus depends on the interruption of the hypothalamohypophysial connections. Male rabbits, however, continued in most instances to show normal libido after transection of the stalk.

Though the functional association of the hypothalamus with the anterior lobe of the hypophysis seems clear, the presence of anatomically demonstrable nerve connections between the two is in dispute. Croll⁶³ and Brooks⁵⁹ both described nerve fibers passing from the infundibular stalk into the pars distalis, but Hair and Mezen⁶⁴ and Rasmussen⁶⁵ denied that this is so. Hair, however, traced a thin distribution of fibers

59 Brooks, C. M. The Study of the Mechanisms Whereby Coitus Excites the Ovulation-Producing Activity of the Rabbit's Pituitary, *Am J Physiol* **121** 157, 1938.

60 Haterius, H. O. Studies on a Neuro-Hypophyseal Mechanism Influencing Gonadotropic Activity, in *Cold Spring Harbor Symposia on Quantitative Biology*, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1937, vol. 5, p. 280.

61 Ingram, W. R. Hypothalamus. A Review of Experimental Data, *Psychosom Med* **1** 48, 1939.

62 Brooks, C. M., and Lambert, E. F. The Effect of Hypophyseal Stalk Transection on the Gonadotropic Functions of the Rabbit's Hypophysis, *Am J Physiol* **128** 57, 1939.

63 Croll, M. M. Nerve Fibers in Pituitary of Rabbit, *J Physiol* **66** 316, 1928.

64 Hair, G. W. The Nerve Supply of the Hypophysis of the Cat, *Anat Rec* **71** 141, 1938. Hair, G. W., and Mezen, J. F. A Study of the Functional Innervation of the Hypophysis, *Endocrinology* **25** 965, 1939.

65 Rasmussen, A. T. Innervation of the Hypophysis, *Endocrinology* **23** 263, 1938.

into the pars tuberalis. Further, he claimed that some of the fibers from the infundibular stalk join company with the sympathetic fibers in the capsule of the gland, which are derived from the pericarotid plexus, and run with them into the pars distalis. Brooks,⁵⁹ in support of his contention of a direct hypothalamohypophysial innervation, described clearcut changes in the cells of the pars distalis after section of the stalk. It has also been shown that destruction of the sympathetic chain, the pericarotid terminations of which are the only other known innervation of the pituitary gland, does not interfere with ovulation in the rabbit.⁶⁰

Whether the nerve impulses from the hypothalamus are delivered to the pars distalis directly through neural connections or by way of an intermediate neurohumoral transmission, as some writers have suggested, the bulk of the available evidence points to an intimate functional and reciprocal relation between the two structures in the activation of the sexual neuroendocrine mechanism.

There are certain observations, however, not altogether compatible with the evidence cited which tend to show that the problem has many complexities not as yet elucidated. We refer especially to a remarkable case in which Dandy⁶⁷ deliberately severed the hypophysial stalk in a young woman to gain better exposure of the chiasmal region in search of a tumor. No tumor was found, however. After this procedure she menstruated regularly and delivered 2 normal children. Perhaps the pars tuberalis with its known hypothalamotuberal connections may in the human being carry on sexual functions after the pars distalis is separated from the hypothalamus. This may possibly explain the occasional persistence of menstruation in women suffering from chromophobic adenomas, in which the functional cells of the anterior lobe of the pituitary gland are presumably destroyed. We have several such instances in our collection of cases of pituitary adenomas. It may even be conceivable that the hypothalamus under certain conditions may carry out certain functions now assigned to the pituitary body, since it has been amply demonstrated by Dandy and Reichert,⁶⁸ among others, that animals may live for years after total hypophysectomy.

66 Hinsey, J. C., and Markee, J. E. Pregnancy Following Bilateral Section of the Cervical Sympathetic Trunk in the Rabbit, *Proc. Soc. Exper. Biol. & Med.* **31** 270, 1933.

67 Dandy, W. E. Section of the Human Hypophyseal Stalk. Its Relation to Diabetes Insipidus and Hypophyseal Functions, *J. A. M. A.* **114** 312 (Jan 27) 1940.

68 Dandy, W. E., and Reichert, F. L. Studies on Experimental Hypophysectomies in Dogs. II. Somatic, Mental and Glandular Effects, *Bull. Johns Hopkins Hosp.* **62** 122, 1936.

The Role of Sex in the Occurrence of Precocious Puberty—Numerous authors have reiterated the statement that precocious puberty due to tumors of or to tumors in the region of the pineal body does not occur in females. In point of fact, Frankl-Hochwait,² who originally delineated the clinical and diagnostic signs for the diagnosis of such tumors, restricted the condition to males. Such a belief is patently false, since there are 2 cases of the condition occurring in females, as indicated in the table of collected cases. Moreover, precocious puberty has been reported in females in several instances in which the third ventricle was affected by distention⁶⁹ or inflammation.⁷⁰ Still one must admit that the overwhelming number of cases occur in males. While an unequivocal explanation for this curious phenomenon is not altogether possible at this time, there are a number of interesting facts which may shed light on it. Lillie⁷¹ many years ago, in his studies on freemartins, came to the conclusion that the earlier activity of the male testes accounted for sexual depression in the female twin. While definitely differentiated interstitial tissue appears shortly after sex differentiation in the fetal calf, pig, rabbit and chick, the homologous tissue does not appear in females until after birth. It would appear, then, in view of present knowledge, that the male testes are prepared earlier in life to respond to the increased activity of the pituitary body which, we believe, results from tumors in the region of the hypothalamus. As a corroboration of this theory it has been found that although the gonadotropic content of the pituitary gland is higher in female infantile animals,⁷² the lesser quantities in the pituitary gland of male infantile animals is due to inhibition of the pituitary gland caused by the presence in the male animals of large amounts of gonadal substances (androgens) consequent on the earlier secretion of these substances.⁷³ Clark⁷⁴ stated that the hypoph-

69 de Cardenas, J. Hidrocefalia y macrogenitosomia precoz, *Pediatría española* **21** 600, 1932. Dorff, G. B., and Shapiro, L. M. Clinicopathologic Study of Sexual Precocity with Hydrocephalus, *Am J Dis Child* **53** 481 (Feb) 1937.

70 (a) Brouwer, B. Observations on the Clinical Patho-Physiology of the Pituitary-Hypothalamic Syndrome, *Psychiat en neurol bl* **6** 699, 1939. (b) Vincent and Kwint, cited by Brouwer.^{70a} (c) Ford, F. R., and Guild, H. Precocious Puberty Following Measles Encephalomyelitis and Encephalitis Lethargica, *Bull Johns Hopkins Hosp* **60** 192, 1937.

71 Lillie, F. R. The Free-Martin. A Study of the Action of Sex Hormones in the Foetal Life of Cattle, *J Exper Zool* **23** 371, 1917.

72 Lawson, H. D., Golden, J. D., and Severinghaus, E. L. The Gonadotropic Contents of the Hypophysis Throughout the Life Cycle of the Normal Female Rat, *Am J Physiol* **125**:396, 1939.

73 Saxton, J. A., and Greene, H. S. N. Age and Sex Differences in the Hormone Content of the Rabbit Hypophysis, *Endocrinology* **24** 494, 1939.

74 Clark, H. M. A Prepubertal Reversal of the Sex Difference in the Gonadotropic Content of the Pituitary Gland of the Rat, *Anat Rec* **61** 175, 1935.

ysis in the male animal may early exercise an inherent capacity for a high rate of secretion but that this is quickly inhibited by the androgenic output of the gonads. If, on the contrary, male rats are castrated at birth, the gonad-inhibiting influences being thus removed, the gonadotropic content of the pituitary gland in the male is equal to or greater than that of the gland in the female.⁷⁵ The conclusion that one is warranted in drawing from these experiments, in application to the phenomenon of *pubertas praecox* as it occurs in association with hypothalamic tumors, is that the male sex is peculiarly more responsive to pituitary hypersecretion because of the earlier development of the gonads. Since appearance of the sexual characters depends directly on the elaboration of the gonadal substances and since the gonads depend on the pituitary gland for activation, the males have a considerable advantage in reacting to excessive pituitary stimulation early in life.

SUMMARY AND CONCLUSIONS

When the pathologic evidence is summarized regarding the occurrence of precocious puberty with lesions in the third ventricle, several facts become evident. First, tumors or other lesions predominantly involving the hypothalamus may be associated with precocious puberty even though the pineal body is unaffected. Second, because of the anatomic position of the pineal body, tumors arising either from it or in its neighborhood almost invariably destroy or compress the posterior portion of the hypothalamus. There is, further, no unequivocal evidence, pathologic or experimental, proving that the pineal body has a secretion or that its extracts have any effect on sexual development. In view of the long-known effects of pathologic and experimental lesions of the hypothalamus on sexual functions, the proposal is submitted that precocious puberty, when occurring under the conditions indicated, is purely a hypothalamic syndrome. We believe that it is a rare variant of sexual disorder, the opposite of the sexual dystrophies so commonly witnessed in the hypothalamic lesions. There is, moreover, a large body of evidence showing that true *pubertas praecox* may be produced in both man and animals by extracts of the anterior lobe of the hypophysis. There is also considerable experimental work demonstrating the functional relationship between the hypothalamus and the *pars distalis* with respect to many sexual activities. The bulk of the experimentation indicates that the hypothalamus controls the release of the gonad-stimulating substances from the *pars distalis*. Investigations pursued with the purpose of locating the portion of the hypothalamus which serves to integrate or

⁷⁵ Clark, H. M. A Sex Difference in the Change of Potency of the Anterior Hypophysis Following Bilateral Castration in Newborn Rats, *Anat. Rec.* **61** 193, 1935.

initiate the several varieties of sexual activity have shown that the posterior portion of the hypothalamus, at least, contains the mechanisms controlling estral behavior and mating. Ovulation has been produced by direct stimulation of the hypothalamus, some authors again producing it by stimulation of the posterior portion of the hypothalamus. Many of these mechanisms are, therefore, located precisely in the area usually affected by tumors which in man result in precocious puberty. Other lesions, such as certain inflammations or ventricular distention which may affect chiefly the gray matter lining the third ventricle, also cause precocious puberty.

A tentative theory of the pathophysiologic basis of precocious puberty when associated with hypothalamic tumors is as follows. Tumors in the posterior portion of the hypothalamus destroy some portion of the mechanism or neural pathways which normally serve to control or inhibit the rate, character or intensity of the nerve impulses passing to the pars distalis. Whether this transmission is directly through neural connections or through indirect neurohumoral intermediation is still uncertain. The pars distalis released from its normal inhibiting control produces or releases excessive amounts of gonadotropic substances. These, in turn, stimulate the ovaries or testicles into hyperactivity. The result of this ovarian or testicular excitation is the production of estrogenic or androgenic substances, which are immediately responsible for the development of the secondary sexual characteristics. The presence of adult quantities of estrogen or androgen in the urines of the patients in the few cases that have been studied from this aspect is indirect proof of hyperactivity of the pars distalis. The endocrine estimations, therefore, support the contention that precocious puberty is due to uncontrolled release of pituitary substances as a consequent manifestation of hypothalamic disturbance, rather than to any hypothetic and as yet unproved pineal secretion. Unfortunately, there have been no experimental lesions placed in the posterior portion of the hypothalamus of young animals in an attempt to produce precocious puberty. The final and conclusive link of evidence is yet to be gathered. It is hoped that investigators will turn their interest in this direction.

NOTE—Since this paper was completed we have located in the literature an additional case of precocious puberty associated with a hypothalamic tumor⁷⁶

The patient, a female infant, began to menstruate regularly at the age of 6 months. At the age of 4 years she had all the bodily characteristics of a mature

⁷⁶ Clark, W. E. L., Beattie, J., Riddoch, G., and Dott, N. M. *The Hypothalamus. Morphological, Functional, Clinical and Surgical Aspects*, London, Oliver & Boyd, 1938, p. 180.

woman She was 9 inches (23 cm) above normal height There were "mental precocity in certain directions" and "secondary sexual characters of a psychic order" At biopsy the presence of mature follicles and corpora lutea was demonstrated in the ovarian material Death occurred in the sixth year from a streptococcic infection Autopsy disclosed a tumor in the interpeduncular space attached to the mamillary bodies and to the area between them and the tuber cinereum There was no hydrocephalus, and the pineal body was intact

The addition of this case makes a total of 17 in which precocious puberty has accompanied a hypothalamic tumor

Dr Raymond Sheely, house officer, performed many of the studies in this case and made a number of translations from the French literature

104 South Michigan Avenue, Chicago

3400 Spruce Street, Philadelphia

CLINICAL STUDIES ON VITAMIN B₁ EXCRETION DETERMINED BY THE FERMENTATION METHOD

HERBERT POLLACK, M D

MAX ELLENBERG, M D

AND

HENRY DOLGER, M D

NEW YORK

The widespread clinical application of vitamin B₁ therapy has been stimulated by the availability of the crystalline substance. Estimates as to dosage and duration of therapy have had to be approximated on the basis of gross clinical changes. The use of this vitamin as a therapeutic test in various confusing syndromes has been expensive to both patient and physician. Furthermore, the negative response to vitamin B₁ in many of these syndromes may discourage its use where it is really indicated.

If a test were available by means of which one could estimate the state of nutrition in a person with respect to vitamin B₁ rapidly and inexpensively, then the clinical application could be placed on a more rational basis.

The methods available up to recently have been long and cumbersome. Schultz, Atkins and Frey developed a method which is comparatively simple and lends itself to clinical investigations.

The details of the actual method of assay have been published¹. In brief, the basis for the test is the stimulating effect of thiamine on the rate of fermentation of dextrose by a yeast. These authors have isolated a yeast strain which, when grown on a fixed medium, will give a definite quantitative response in rate of fermentation to the presence of thiamine within certain limits of concentration. This test is sensitive to the presence of thiamine in any and all of its known forms. It is also sensitive to the presence of the pyrimidines, which will give mole for

From the Medical Services, Metabolism Clinic and the Division of Laboratories of the Mount Sinai Hospital

1 Schultz, A. S., Atkins, L., and Frey, C. N. Fermentation Test for Vitamin B₁, *Science* **88** 547, 1938, *J. Am. Chem. Soc.* **59** 948 and 2457, 1937, Influence of Nicotinic Acid on the Fermentation Method for Vitamin B₁ Determination, *ibid* **60** 1514, 1938.

mole acceleration of fermentation, comparable with that given by thiamine. One of the sources of pyrimidine in the urine is undoubtedly the vitamin B complex.

REPORT OF INVESTIGATIONS

A series of estimations of vitamin B₁ were made on samples of urine excreted by a group of normal persons at two hour intervals during the working day and on one complete overnight sample. It was apparent that the postprandial collections of urine contained the largest amounts of vitamin B₁. This was related to the vitamin B₁ content of the previously ingested meal. Furthermore, the vitamin B₁ content of the urine collected during the fasting overnight period was fairly constant for any one person if the collections were started at least four hours after the evening meal. The urines of a group of several malnourished patients with symptoms suggestive of vitamin B₁ insufficiency were also assayed. It was found that their overnight excretions were considerably less than those of the normal controls. The next logical step was to determine the differences in excretion between two such groups after the administration of thiamine hydrochloride parenterally. A preliminary survey immediately showed the possibility of using the response to a standard load as a test for the state of nutrition with respect to vitamin B₁.

The actual load test finally evolved may be described in brief as follows. The patient is instructed to have his evening meal at the usual time. He is told not to eat pork, chicken, liver, leguminous vegetables or nuts at this meal. Four hours after this meal he is to void and discard the urine. All urine voided from then up to and including 9 a. m. the next morning is saved as one sample. At this time he is given an injection of thiamine hydrochloride intramuscularly. All urine voided for the next four hours is collected as one sample. The patient is encouraged to drink one to two glasses of water during this period in order to insure an adequate volume of urine. No breakfast is permitted, the patient being kept in the fasting state until the four hour sample of urine is obtained. Both the overnight and the postinjection four hour sample were assayed for vitamin B₁ content. This report deals with the results obtained from the postinjection samples^{1a}. The data obtained from the overnight excretions will be discussed in a later report.

The routine of the test as presented in this form was based on the attempt to avoid many of the difficulties encountered in earlier experiences. A four hour collection of urine is comparatively simple for any

1a Pollack, H., Dolger, H., Ellenberg, M., and Cohen, S. A Test Proposed to Measure Vitamin B₁ Saturation in Humans, *Proc Soc Exper Biol & Med* **44** 98, 1940.

patient to carry out. The fasting state of the test rules out inconsistencies of diet. It was our experience that to attempt to collect twenty-four hour samples of urine, both from ambulatory and from hospital patients, entailed many errors. The ambulatory patient cannot eat a constant diet without subjecting himself to many inconveniences. The intramuscular injection of the thiamine was chosen in preference to the oral administration to insure rapidity and constancy of absorption in order to make the use of a four hour period valid. Marrack and Hoellering² have also found that when thiamine was injected intramuscularly it was excreted almost entirely within the first three hours after injection and there was little or no residual excretion to be observed in the subsequent three hours.

Obviously, the renal factor is important in any test dependent on urinary excretion. Table 1 illustrates the ability of the kidney to con-

TABLE 1—*Relationship of the Volume Output of Urine to the Excretion of Thiamine*

Patient	Volume of Urine, Cc	Vitamin B ₁ Content, Micrograms per Cc	Total Micrograms of Vitamin B ₁ Excreted
D V	213	0.54	115
A D	654	0.24	152
L P	714	0.27	193
B S	227	0.98	222
S S	192	1.19	228
A K	78	3.14	245
F R	795	0.34	270
A A	90	3.13	282
E D	148	2.03	301
D C	1,072	0.32	342
F P	163	2.55	416

centrate, over a wide range, the substances in the urine which give vitamin B₁ activity. It is definitely seen that the amount excreted is independent of the volume of urine in the presence of normal renal function, as Marrack and Hoellering² also observed.

In order to determine the most satisfactory dose of thiamine hydrochloride for a load test, the responses to varying doses in the same patients were studied. Twenty-one patients were observed in this way. The amounts injected were 1, 2, 5, 10 and 20 mg. of thiamine hydrochloride, respectively, at approximately one week intervals. The data from these responses are presented in table 2 and in figure 1. Figure 1 shows the amount recovered in the urine plotted as a percentage of the amount injected. The response to any one dose in any patient remains at the same comparative level as that for all other doses. Thus, a low response to an injection of 1 mg. is associated with a relatively low

² Marrack, J. H., and Hoellering, H. F. Excretion of Injected Aneurin (Vitamin B₁), *Lancet* 1 325, 1939.

TABLE 2—*Excretion of Substances with Vitamin B₁ Activity, Expressed in Micrograms, in Urine Collected During Four Hour Interval After Injection of Thiamine Hydrochloride*

Patient	Mg of Thiamine Hydrochloride Injected				
	1	2	5	10	20
1	260	505	1,521	4,092	
2	146	444	1,040	3,100	
3	120	194	647	1,910	
4	144	271	940	2,230	
5	187	360	1,255		
6	132	230	1,170		
7	191	520	1,855	4,230	
8	153	310	1,132	2,780	5,490
9	230	473	1,320	4,120	
10	202	343	1,222	2,880	
11	275	501	1,950	4,375	
12	244	614	1,780	3,910	
13	123	275	1,190	3,172	
14	238	322	1,376	3,330	
15	210	315	1,210	3,220	
16	121	180	785	2,673	
17	336	485	1,950	4,000	
18	195		1,240	3,070	
19	191		945	2,610	
20	245			3,000	7,800
21	230			2,850	6,900

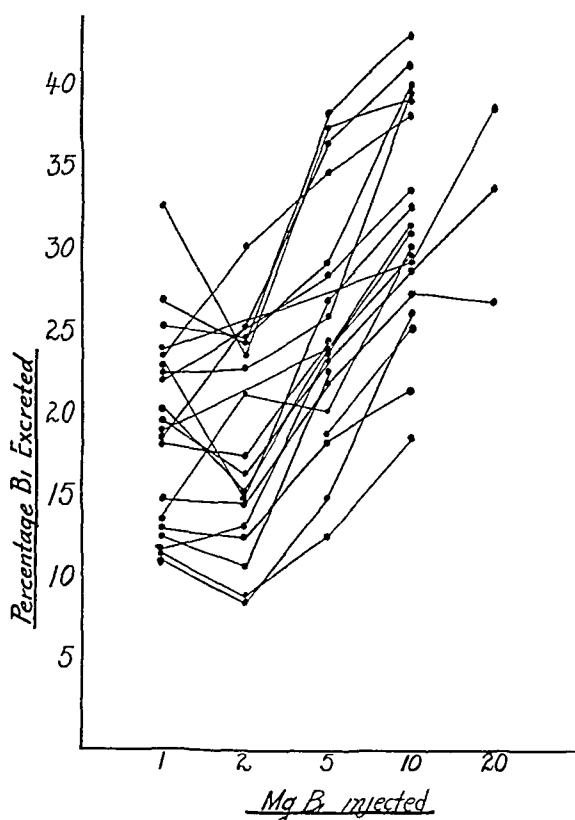


Fig 1—Amounts of vitamin B₁ excreted in the urine of 21 unselected patients after injection of thiamine hydrochloride

response to any of the other amounts injected. In addition to these relative values, the absolute amount excreted increases as the dose. When calculated on a percentage basis, as plotted in figure 1, the series of injections of 1 and 2 mg do not fall in line with the others. This can be explained as follows. There is a definite excretion of substances giving B₁ activity, as measured by the fermentation method, in the urine of normal persons at all times. By actual measurement, under the comparable conditions of the experiment (i.e., overnight fasting and no breakfast) a four hour sample of urine will yield from 40 to 100 micrograms of substances showing vitamin B₁ activity, depending on the state of nutrition of the subject. This represents the basal, or

TABLE 3—Comparison of the Excretion of Vitamin B₁* by the Same Person at Different Times After the Injection of 1 Mg of Thiamine Hydrochloride

Patient	First Test	Second Test
M F	100	133
D B	115	125
J S	105	116
M G	113	129
L C	120	110
R K	128	165
B G	141	144
S B	170	201
E H	171	185
A B	200	188
S L	204	214
M D	209	252
C L	205	226
M E	215	231
B S	222	199
L L	296	271
J S	315	302
S W	336	381
G S	355	328

* The excretion is expressed in terms of micrograms of substances with vitamin B₁ activity excreted in four hours

endogenous, excretion and forms an appreciable percentage of the substances with vitamin B₁ activity present in the urine after the injection of 1 or 2 mg of thiamine hydrochloride. After an injection of 5, 10 or 20 mg its relative importance decreases.

The urinary excretion after an injection of 1 or 2 mg may indicate that (1) this dose is within the physiologic range of utilization, (2) such a dose reflects the ability of the body to retain injected thiamine and (3) the endogenous excretion of substances with B₁ activity is a measurable portion of the total amount excreted. The endogenous excretion alone may be misleading and dependent on the recent dietary intake. The response to the load test, however, is a better indication, as it reveals the more prolonged deficiencies.³

3 Smith, K. A. Thiamin and Diabetes Mellitus, Proc. Staff Meet., Mayo Clin. 5:529, 1940. Robinson, W. D., Melnick, D., and Field, H., Jr. Urinary

(Footnote continued on next page)

Before any clinical use could be made of this response to a test dose the constancy of response of any one person had to be determined. To establish this point the urinary excretion of substances with B_1 activity by 19 unselected subjects after an injection of 1 mg of thiamine hydrochloride was determined. This procedure was repeated on these 19 subjects after a two week period. Table 3 summarizes the results. The constancy was well within the biologic variations.

From this preliminary work it was decided that the response to the injection of 1 mg of thiamine hydrochloride might have some clinical application. Thirty-one normal university students, instructors and physicians were subjected to the test, the response to the injection of 1 mg of the drug being used as the standard. In addition, 408

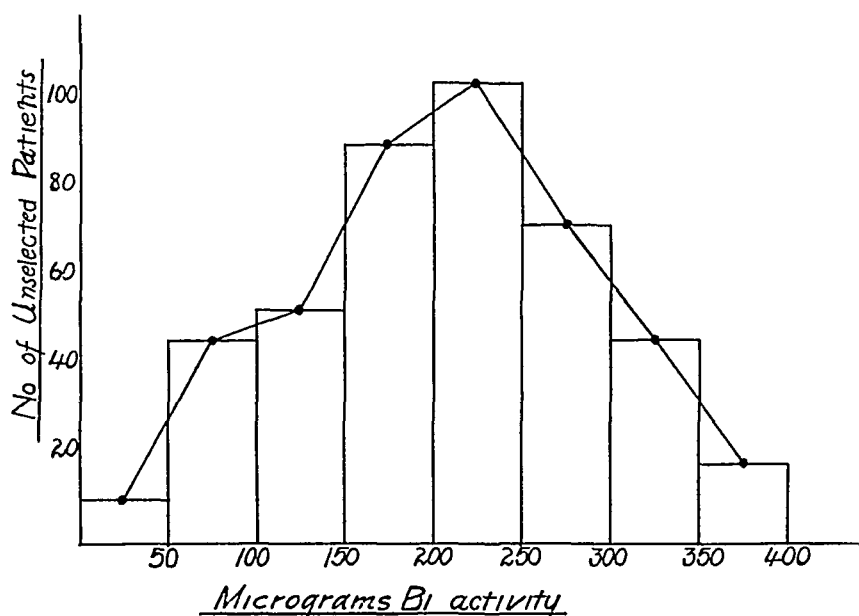


Fig 2—Distribution curve of urinary excretion by 439 unselected subjects, four hours after the injection of 1 mg of thiamine hydrochloride, of substances showing B_1 activity (measured in micrograms)

unselected patients from the wards and the dispensary were subjected to this procedure. It should be remembered that these patients are not to be considered as representing a cross section of the general population. Because of existing illness one would expect to find a higher percentage of vitamin B_1 unsaturations in this mixed group than in a perfectly normal one. The results of the tests in this group are plotted in figure 2.

Excretion of Thiamin in Clinical Cases, *J Clin Investigation* **19** 399, 1940 Melnick, D., Field, H., Jr., and Robinson, W. D. Quantitative Chemical Study of the Urinary Excretion of Thiamin by Normal Individuals, *J Nutrition* **18** 593, 1939 Borson, H. Clinical Application of the Thiochrome Reaction in the Study of Thiamin Deficiency, *Ann Int Med* **14** 1, 1940 Holt, L. E., Jr., and Najjar, V. A. Studies in Thiamin Excretion, *Bull Johns Hopkins Hosp* **67** 107, 1940

Table 4 presents the data on the group of 439 persons, with their clinical conditions separated into nine categories. Table 5 is a brief statistical analysis of some of these data, which is shown to prove their validity. The persons excreting from 200 to 250 micrograms of B₁ active substance in the four hour postinjection period represent the mean of the tested group. The shape of the curve of distribution is

TABLE 4—*Effect of Injection of 1 Mg of Thiamine Hydrochloride on the Urinary Excretion of Vitamin B₁ Classified in 50 Microgram Steps in Four Hundred and Thirty-Nine Subjects*

Category	Vitamin B ₁ Excreted, Micrograms								Total
	0 to 50	51 to 100	101 to 150	151 to 200	201 to 250	251 to 300	301 to 350	351 to 400	
Normal health				3	3	14	8	3	31
Diabetes mellitus	1	3	9	30	44	24	23	5	139
Renal insufficiency, congestive heart failure	4	4	2	7	1			1	19
Gastrointestinal disease	3	11	10	13	7	2	1	1	48
Alcoholism		2	2						4
Miscellaneous disease	1	17	22	29	46	29	12	6	162
Disease of the liver and gall bladder			3	3		3		1	10
Infection	1	3	3	5	3	1	3	2	21
Ariboflavinosis	4		1						5

TABLE 5—*Statistical Analysis of the Data*

Category	Mean	Standard Deviation	Number of Subjects	Standard Deviation of Mean
Normal health	278	81.8	29	15.4
Diabetes mellitus	233.8	73.2	150	6.0
Miscellaneous diseases	213.3	92.5	106	7.2
Gastrointestinal disease	153.3	76.5	51	10.9
Infection	221.5	107.7	23	22.9
Total of 457 subjects	213.6	91.2	457	4.3

probably affected in the region of the 100 to 150 microgram excretion level by the presence of such a large number of chronically ill persons who have been on voluntarily or otherwise restricted diets.

Because of the known relationship of vitamin B₁ to carbohydrate metabolism, it has been inferred that diabetes mellitus might represent a deficiency of this vitamin. Included in the large series of patients previously mentioned were 139 with diabetes mellitus. Figure 3 represents the curve of distribution of the excretion responses of the latter

patients The mean falls in the same range as that of the large unselected group There were fewer low responses among the patients with diabetes than among persons in the large group

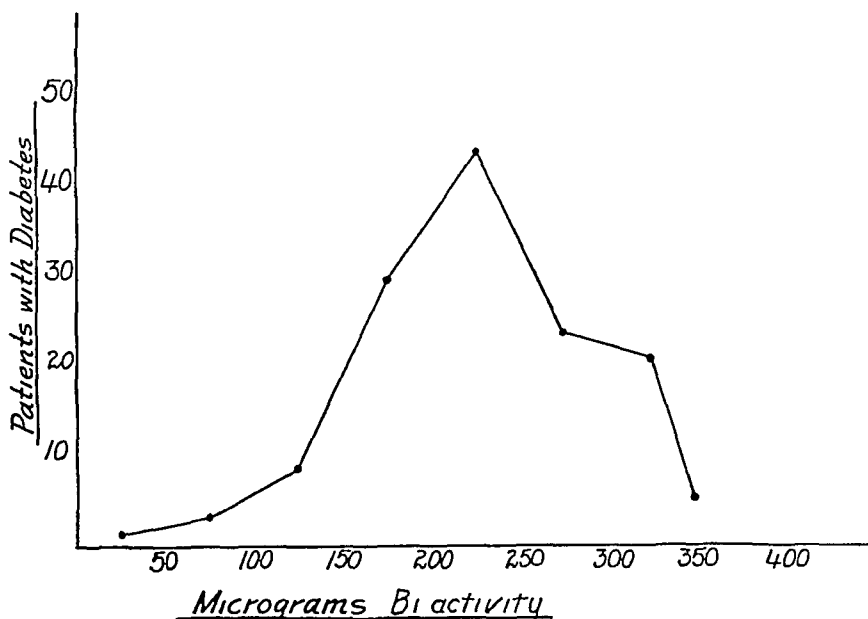


Fig 3—Distribution curve of urinary excretion by 139 patients with diabetes of substances showing vitamin B₁ activity (measured in micrograms)

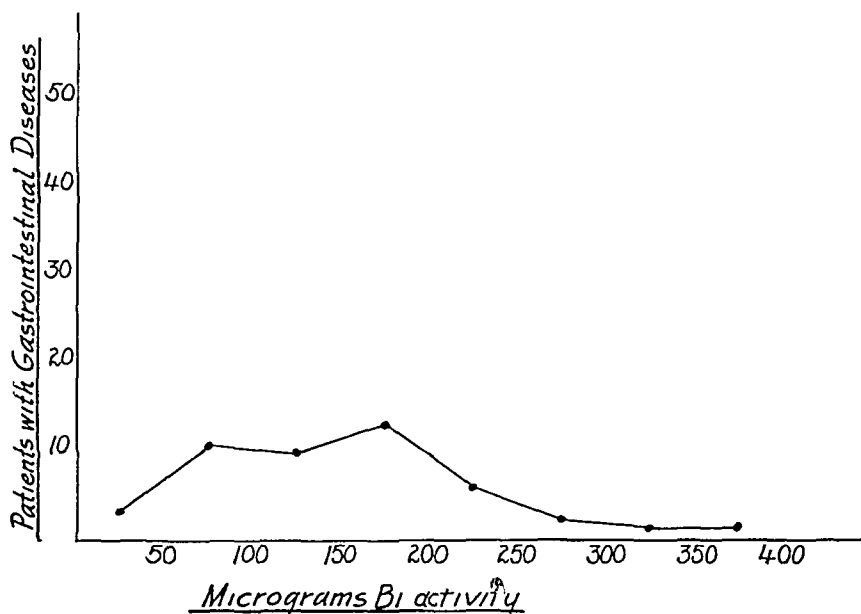


Fig 4—Distribution curve of urinary excretion by 48 patients with gastrointestinal diseases of substances showing vitamin B₁ activity (measured in micrograms)

Figure 4 shows the distribution curve of the response to the injection of 1 mg of thiamine hydrochloride of 48 patients with gastrointestinal diseases This curve and the statistical analysis of the data leave little

doubt that persons with such diseases are especially prone to vitamin B₁ deficiencies. Such a conclusion has been suspected from clinical evidence contributed by numerous authors.

TABLE 6—Data on Patients Showing Low Excretion Response

Patient	Tolerance, Excretion of Vitamin B ₁ After Test Dose, Micrograms	Diagnosis	Comment
C B	145	Polycystic kidneys, renal calculi, malnutrition	
F C	150	Cholecystitis	
S C	149	Thyrotoxic heart disease	Post thyroidectomy
L G	134	Obesity	Strict reducing diet
M	135	Moderate alcoholism	No manifest deficiency
L B	85	Sprue	Age 72
A D	155	Gastrointestinal neurosis	Anorexia
R E	16 4	Malignant nephrosclerosis	Uremia, absolute renal insufficiency
R E	109	Pernicious anemia	Age 74
M F	100	Rheumatic chronic cardiovascular disease	Active carditis
R G	131	Renal calculi, pyelitis of right kidney	Tolerance normal (265 micrograms) when test was repeated after discharge
M G	73 6	Lobar pneumonia, hepatic calculi, pernicious anemia	
J G	95	Cardiac disease	Age 62
A H	85	Extreme essential hypertension	
J J	100	Melanosarcoma, pentosuria	
L K	71	Chronic fibroid tuberculosis	Tolerance normal (279 micrograms) when test repeated five months later, and discharge after therapy
P M	69	Gout, arteriosclerosis	Age 61, tolerance 154 micrograms when test repeated with patient on a high carbohydrate diet
J M	112	Essential hypertension, anginal syndrome	Tolerance 158 micrograms when test repeated five months later, after discharge
P P	148	Cirrhosis of liver	
G P	146	Abdominal pain, gastric ulcer?	
M R	98	Chronic glomerulo nephritis	
M S	153	Arteriosclerosis, gout, anginal syndrome	
M R	88	Arteriosclerosis, hypertension, heart disease, prostatic disease	
J S	105	Arteriosclerosis, sacro iliac disease	Age 62, tolerance 116 micrograms when test repeated in five months
M S	130	Coronary sclerosis, fibrosis, vitamin B deficiency	Age 60, tolerance 162 micrograms when test repeated
H S	138	Sinusitis, folliculitis of left axilla	Acute illness, tolerance 270 micrograms when test repeated after recovery
S T	138	Hypertension, arteriosclerosis	
D V	115	Coronary sclerosis, cystitis, postnephrectomy	
E W	92	Bronchial asthma	
L C	120	Jejunal ulcer	Prolonged Sippy diet regimen

Tables 6 and 7 present brief clinical data on those patients whose vitamin B₁ excretion responses fall in the lower levels.

Earlier in this paper reference was made to the possible effect of renal function on the validity of this type of test. In table 4 the results of this test on 19 patients with congestive heart failure are recorded.

The results uniformly fall below 200 micrograms. Knowing that circulatory failure secondarily affects renal function, one must exercise caution in the interpretation.

In table 4 it might be of interest to point out that on the basis of this test, if excretion levels below 150 micrograms in four hours are to be taken as indicating thiamine deficiency, then of 31 normal persons all had a greater excretion response and 13, or 9 per cent, of 139 patients

TABLE 7—*Data on Patients with Diabetes Mellitus Showing Low Excretion Responses*

Patient	Tolerance, Excretion of Vitamin B ₁ After Test Dose, Micrograms	Comment
F A	108	Man aged 80 with edema and congestive heart failure, edema out of proportion
M E (1 mg)	88	Age 59, achlorhydria, inadequate diet
(2 mg)	213	
S E	151	Woman aged 25, treated in Boston three years previously for nutritional deficiency, diabetes retinitis
G F (1 mg)	153	Diet of 800 calories
(2 mg)	310	
L F	138	Woman aged 58, chronically ill and malnourished
M G	113	Hypertension, negative Wassermann reaction with neurologic changes
J B	48	Diabetes, hypertension, nephrotic syndrome
E G	48	Arteriosclerosis, malnutrition, subnormal weight
L N (1 mg)	151	Prolonged polyuria, postencephalitic syndrome
(2 mg)	322	
B H	72	Hypertension, spondylitis, chronic illness
R K	128	Hypertension, cardiovascular disease, arthritis, inadequate diet
B K	120	Woman aged 77
L M	80	Arteriosclerosis, subnormal weight, malnutrition
F M (1 mg)	115	Woman aged 73 with arthritis
(2 mg)	360	
B M	125	
H M	147	Man aged 65 with bilateral cataracts
S R	35	Woman aged 65 with congestive heart failure and a clinical diagnosis of beriberi heart
D S	160	Malnutrition, possible gastrointestinal lesion
H S	155	Test made immediately after an episode of ketosis

with diabetes mellitus, 24, or 50 per cent, of 48 patients with gastrointestinal diseases, 4, or 100 per cent of 4 patients with alcoholism, 40, or 25 per cent, of 162 patients with miscellaneous diseases, 3, or 33 per cent, of 10 patients with disease of the liver and gallbladder, 7, or 33 per cent, of 21 patients with infections and 5 of 5 patients showing other evidence of vitamin B complex deficiencies were poorly supplied with thiamine.

COMMENT

Other investigators² using totally different methods have observed the same general trend as that shown in the foregoing paragraph. The

absolute values in thiamine excretion studies based on the thiochrome or the diazotized amine technic are much lower than those based on the fermentation method. The validity of any assay of vitamin B₁ work is entirely dependent on the accuracy of the method used for the determination of B₁ active substances in the urine. Schultz, Atkins and Frey have shown that besides thiamine itself, only the pyrimidines, more specifically the 2-methyl-5-ethoxymethyl-6-amino pyrimidine, will give this fermentation response. As pointed out by Schultz, Light and Frey, "irrespective of whether or not the urine or feces responses after the oral administration of thiamine obtained represent true vitamin B₁, there is a close correlation between the determined values and the B₁ intake." The pyrimidines in the urine probably represent in part at least that fraction of the thiamine metabolized in the body. Were it possible to separate completely the thiamine from the pyrimidine in the urine, one would have a better measurement of the actual utilization.⁴ For the purposes of clinical evaluation, however, such an absolute determination is not necessary. The relative figures given by this test undoubtedly have clinical importance. In addition, it might also hold true that this fermentation method, because of its nonspecificity for pure thiamine, i.e., the response to pyrimidine (the breakdown products), may give a more complete picture than the specific chemical assays.

The preceding results have shown that there are great variations in response to the administration of 1 mg of thiamine hydrochloride. Statistical analysis of the data on 457 subjects showed that 75 per cent of the persons tested excreted more than 150 micrograms of substances showing vitamin B₁ activity as measured by the yeast fermentation method. Clinical analysis of the cases of those persons with an excretion falling below the 150 microgram level reveals the existence of certain factors. These include anorexia, diarrhea, poor dietary intake, alcoholism, debilitating illnesses, prolonged toxic states and hepatic dysfunction. It has been pointed out by Jolliffe and others that all of these factors are frequently associated with vitamin B₁ deficiencies. This correlation helps to substantiate the inference that the response to the proposed 1 mg load test may be of value in detecting the subclinical states of vitamin B₁ deficiency.

SUMMARY

The fermentation test of Schultz, Atkins and Frey for vitamin B₁ is clinically applicable because of its simplicity and rapidity.

The rationale for the development of the response to the 1 mg load test is discussed.

⁴ Recent work with the combined thiochrome and fermentation methods bears out this contention.

The results of the application of this test to patients with various clinical syndromes and to normal persons are presented

This test would appear to be of value in detecting the subclinical states of vitamin B₁ deficiency

The reliability of the test being assumed, this evidence indicates that 25 per cent of 389 patients with various diseases, excluding renal insufficiency and including alcoholism (4 instances), were insufficiently supplied with thiamine

Dr C F Frey, of the Fleischmann Laboratory, gave us the yeast

CLINICAL STUDIES ON BLOOD DIASTASE

I LOW BLOOD DIASTASE AS AN INDEX OF IMPAIRED HEPATIC FUNCTION

S H GRAY, M D

J G PROBSTEN, M D

AND

CARL J HEIFETZ, M D

ST LOUIS

In other communications from this laboratory the normal diastase values¹ and the significance of elevated blood diastase² were discussed. The accurate assay of subnormal amounts of diastase afforded by the Somogyi technic³ revealed that subnormal diastase values were far more frequent than were increased values. In preliminary reports⁴ it was pointed out that low blood diastase values seemed to be indicative of impaired hepatic function. Analysis of the considerable material that we have accumulated, which forms the basis of this study, supports this early interpretation. Other investigators using the Somogyi technic have corroborated this concept⁵.

Aided by the David May-Florence G May Fund

From the laboratory and the Department of Surgery, Jewish Hospital, and the Department of Surgery, Washington University School of Medicine

1 Somogyi, M Diastatic Activity of Human Blood, *Arch Int Med* **67**: 665 (March) 1941. Somogyi stated "The terms diastase and amylase are often used interchangeably. I prefer the term diastase to denote the enzyme dealt with in this study, an enzyme which is not only an amylase, but a glycogenase and a dextrinase as well."

2 Heifetz, C J, Probst, J G, and Gray, S H Clinical Studies on Blood Diastase II Significance of Increased Blood Diastase, *Arch Int Med*, this issue, p 819

3 Somogyi, M Micromethods for the Estimation of Diastase, *J Biol Chem* **125** 399, 1938

4 (a) Somogyi, M Blood Diastase as an Indicator of Liver Function, *Proc Soc Exper Biol & Med* **32** 538, 1934 (b) Gray, S H, and Somogyi, M Relationship Between Blood Amylase and Urinary Amylase in Man, *ibid* **36** 253, 1937

5 Rachmilewitz, M Clinical Significance of Blood Diastase in Diseases of the Liver and Bile Ducts, *Harefuah* **12** 111, 1937, Blood Diastase in Hepatic and Biliary Disease, *Am J Digest Dis* **5** 184, 1938 Cole, W H Acute Pancreatitis, with Special Reference to Pathogenesis and the Diagnostic Value of the Blood Amylase Test, *Am J Surg* **40** 245, 1938

We are unable as yet to offer any valid explanation of the decrease in blood diastase associated with impaired hepatic function. If diastase were found in the liver, one could assume that the production of the enzyme is one of the functions impaired when the liver is affected. But, as was discussed previously,¹ there is no basis for the assumption that liver tissues produce or even contain diastase. It should be kept in mind that we employ the term "hepatic function" only in a general sense.

Various workers have reported abnormally high levels of blood diastase in cases of diseases of the biliary tract, acute obstruction of the common bile duct,⁶ disease of the gallbladder,⁷ and catarrhal jaundice.⁸ In the light of our observations, however, it is likely that in most of these reported cases acute pancreatic involvement was the actual cause of the increased diastatic activity, in some instances renal insufficiency might have been discovered as the cause had the urine diastase-blood diastase ratio been determined.²

Several workers have found that jaundice per se does not change the level of the blood diastase.⁹ These observations have been verified in our laboratory. The addition of bile to blood, either in vitro or in vivo (by ligation of the common bile duct), caused insignificant if any changes in the blood diastase level in experimental animals. This would be expected, since under normal conditions hepatic bile is practically devoid of diastatic activity.¹⁰ According to our observations, the diastatic activity of blood in cases of disease of the biliary tract tends toward subnormal levels, probably as a result of involvement of

6 (a) Millbourn, E. On the Diastasic Conditions in Cases of Jaundice Due to Cholelithiasis, Acute Hepatitis, and Malignant Tumors, *Acta chir Scandinav* **77** 523, 1935. (b) Foged, J. The Diagnostic Value of Urine Diastase, *Am J Surg* **27** 439, 1935. (c) Branch, C. D., and Zollinger, R. The Value of Blood Diastase in the Diagnosis of Common Duct Stone, *ibid* **41** 233, 1938.

7 (a) Cohn, E. Ueber den Wert der Diastasebestimmung im Serum und Urin bei Pankreasaffektionen im Anschluss an Erkrankungen der Leber und der Gallenwege, *Arch f Verdauungskr* **39** 199, 1926. (b) Kaczander, P. Zur Diagnostik der Pankreasaffektionen mittels der Wohlgemuthschen Diastaseprobe im Urin, *Deutsche med Wchnschr* **57** 1103, 1931. (c) Millbourn.^{6a}

8 Cameron, G. Studies on Diastatic Activity. II. The Action of Bile on the Enzyme Diastase, *J Metab Research* **5** 243, 1924. Cohn.^{7a}

9 (a) Stocks, P. The Quantitative Determination of Amylase in Blood Serum and Urine as an Aid to Diagnosis, *Quart J Med* **9** 216, 1916. (b) Elman, R., Arneson, N., and Graham, E. A. Value of Blood Amylase Estimations in the Diagnosis of Pancreatic Disease, *Arch Surg* **19** 943 (Dec, pt 1) 1929. (c) Fricker, E. Untersuchungen über den Harnamylasegehalt beim gesunden und kranken Menschen, *Schweiz med Wchnschr* **56** 129, 1936. Millbourn.^{6a} Foged.^{6b}

10 (a) Zucker, T. F., Newburger, P. G., and Berg, B. N. The Amylase of Serum in Relation to Function States of the Pancreas, *Am J Physiol* **102** 209, 1932. (b) Popper, H. L. Pankreassaft in den Gallenwegen, *Arch f klin Chir* **175** 660, 1933.

the liver. The occasional finding of an elevated blood diastase level points to probable acute pancreatic involvement, a well known occurrence in disease of the biliary tract¹¹. The fall in blood diastase level is always accompanied by a decrease in the urinary excretion of the enzyme, although the parallelism between the two changes is not strict.

Blood diastase determinations were performed in this laboratory on patients with all types of disease admitted between 1933 and 1938 to the Jewish Hospital of St. Louis, a general hospital for patients with acute conditions, excluding contagious and mental diseases. As in most statistical analyses, certain limitations had to be stipulated in the treatment of our material. Thus, because in the majority of cases we performed but one diastase determination, in our compilation we used only the first values in those cases in which repeated determinations were carried out. Since it was in the latter category of cases that the blood diastase values exhibited particularly great deviations from the normal, the statistical results do not always represent the extremes in variations. Had we tabulated the maximum changes, the percentage of low diastase levels would have been, as a matter of fact, greater than the charts indicate. In cases in which a new illness developed during the period of hospitalization the first determination after the onset of the illness was used. Decisions were sometimes difficult in cases with two or more diagnoses. After careful consideration of the history, the case was classified under the disease considered to be the dominant one. When two or more diseases were apparently of equal importance, our experience as regards the diseases which were known to affect the diastase values naturally influenced our judgment in the classification. Cases in which the patients were readmitted were dealt with as new cases.

For the convenience of the reader, it may be pointed out here that normal diastase values, determined by the Somogyi technic, range between 80 and 150, values between 60 and 80 and between 150 and 180 are on the borderline of normal. Values below 60 are considered definitely subnormal (fig. 1A).

DISEASE OF THE BILIARY TRACT

A compilation of the diastase levels determined in 410 cases of disease of the biliary tract included those determined in 235 cases of diseases of the liver and the bile ducts and in 175 cases of diseases of the gallbladder. A comparison of the two groups, shown in figure 1B and C, reveals that a greater percentage of subnormal levels is found in cases of disease of the liver and bile ducts. While some degree of functional, and even pathologic involvement of the liver is often present

¹¹ Gray, S. H., Probstein, J. G., and Heifetz, C. J. Transient Acute Pancreatitis, *Ann. Surg.* **108**: 1029, 1938.

in cholecystic disease,¹² the impairment of hepatic function is not extreme. Involvement of the liver and the bile ducts, on the other hand, causes definite and extensive diminution of hepatic function.

Diseases of the Liver and the Bile Ducts—The 235 cases of involvement of the liver and the bile ducts included 16 cases of single or multiple hepatic abscesses, 26 of acute catarrhal jaundice, 52 of obstruction of the common bile duct, 73 of malignant conditions of the liver and the bile ducts, 29 of cirrhosis of the liver, 30 of enlargement of the liver of undetermined origin and 9 of miscellaneous diseases of the liver. The last subgroup included cases of acute yellow atrophy, toxic hepatitis and fatty infiltration associated with cachexia of a malignant condition.

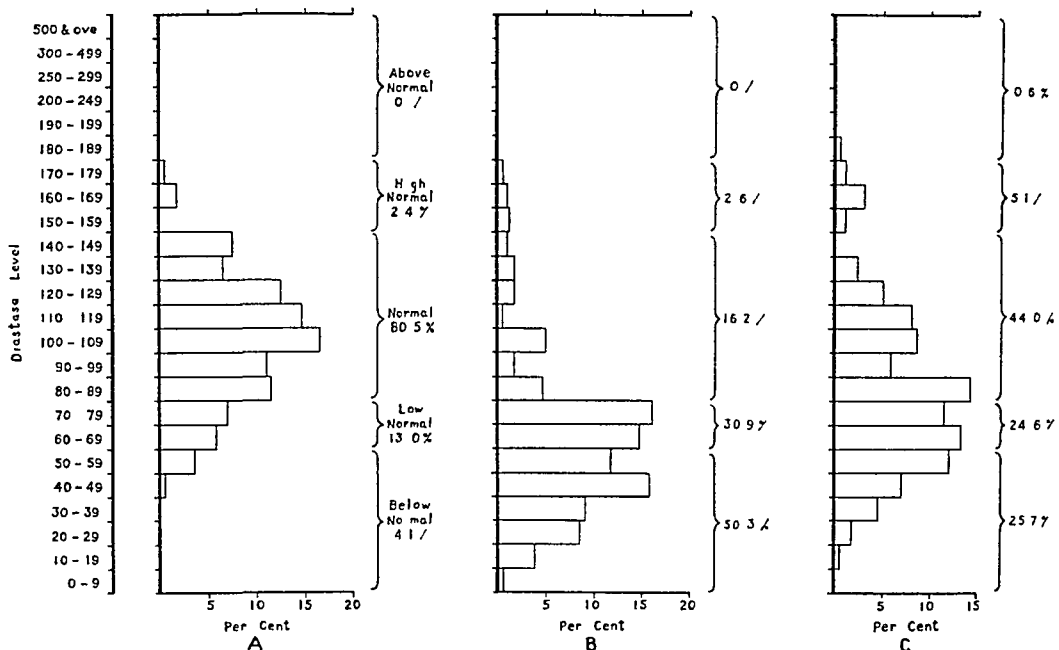


Fig 1—Blood diastase levels in (A) a group of 170 healthy normal persons, (B) 235 cases of diseases of the liver and the bile ducts and (C) 175 cases of disease of the gallbladder.

In all these subgroups a tendency in the direction of subnormal diastatic activity was manifest. The most notable decreases occurred in cases of abscess of the liver and of a malignant condition.

In many of the cases of obstruction of the common bile duct there was concomitant disease of the gallbladder, but for statistical purposes these cases are included under the former condition. Of the 52 cases, disease in 19 resulted from stenosis, in 14 from calculi, in 8 from tumors and in 11 from undetermined causes. Because of the small number of cases in each subgroup, separate tabulations were considered.

¹² Graham, E. A., Cole, W. H., Copher, G. H., and Moore, S. *Diseases of the Gall Bladder and Bile Ducts*, Philadelphia, Lea & Febiger, 1928.

inadvisable. In general, however, differences between the subgroups were not sufficient to lend significance to the etiologic factors.

Of the 73 cases of malignant conditions of the liver and the bile ducts, in 9 the disease was primary, in 44 secondary or metastatic and in 20 probably malignant. The last subgroup was composed of cases in which there were unmistakable signs of a malignant condition elsewhere than in the liver, with evidence of hepatic involvement unproved by either operation or autopsy. It is notable that in all 9 cases of a primary malignant condition of the liver and the bile ducts the diastase values were below 60.

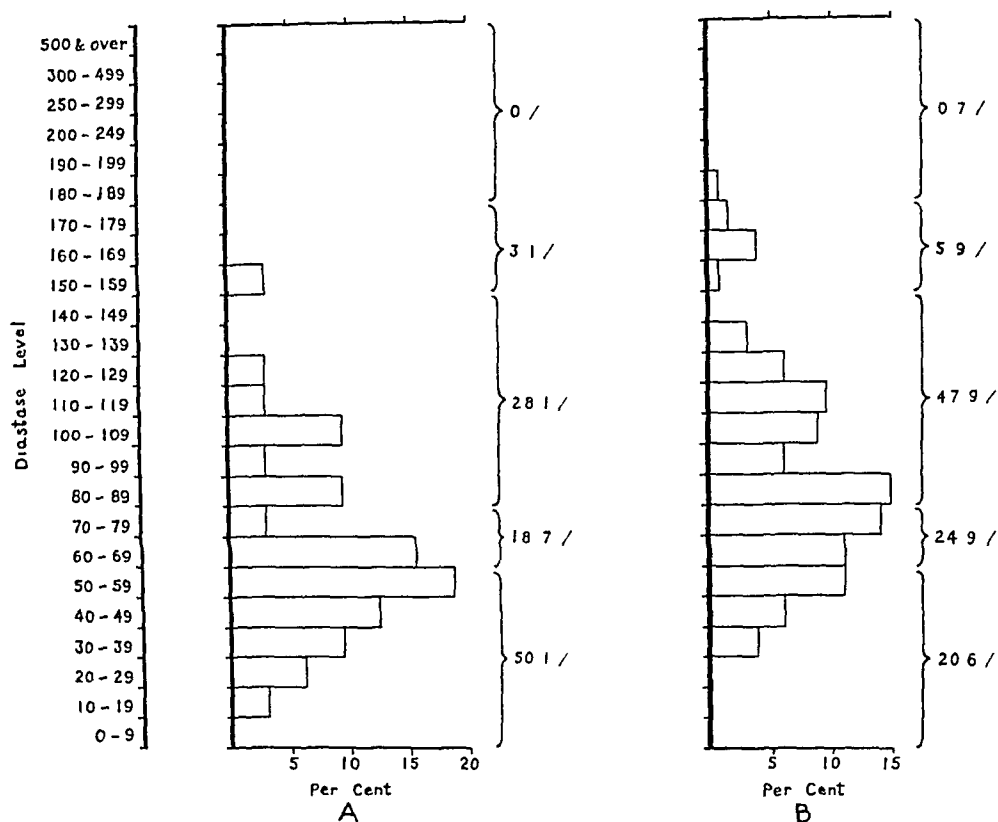


Fig 2—Blood diastase levels in (A) 32 cases of acute cholecystitis and (B) 136 cases of chronic cholecystitis.

Diseases of the Gallbladder—The 175 cases of cholecystic diseases included, as was previously mentioned, none in which there was evidence from operation or autopsy of obstruction of the common bile duct. There were 32 cases of acute cholecystitis, 136 of chronic cholecystitis and 7 of primary tumors of the gallbladder. A comparison of A and B in figure 2 shows that acute cholecystitis tends to cause a greater lowering of the diastase level than does chronic cholecystitis. Acute infections seem to exert on the liver, therefore, a more severe toxic effect than do chronic infections, as is the case with acute toxic lesions in general (see following section).

Of the 136 cases of chronic cholecystic disease, the gallbladders in 76 were proved at operation to contain calculi and in 7 no calculi were found. In 53, in which operation was not performed, there was clinical or roentgenologic evidence of chronic cholecystitis. While in all three subgroups there was a definite tendency toward subnormal diastase values, a great number of values fell well within the normal range.

DISEASES AND CONDITIONS INDIRECTLY AFFECTING THE LIVER

Infections—The role of the liver as a detoxifying agent in all types of infections is well known. Any infection eliciting a systemic response undoubtedly brings into play the functional defenses of the liver. As a result of these responses, and depending on the toxicity and duration of the infection, cloudy swelling, fatty degeneration and necrosis may or may not result.¹³ It is well known that these changes occur in many cases of pneumonia, typhoid fever, streptococcic infections and septicemia. However, whether or not these changes are demonstrable, it is probable that the functional capacity of the liver is impaired. It was not surprising, therefore, that in many of the cases of both generalized and localized infections there were subnormal diastase values. Figure 3A summarizes the diastase levels determined in 147 cases of acute generalized and 440 cases of acute localized infections. The former included 3 cases of acute rheumatic fever, 12 of malaria, spontaneous or artificially induced, 13 of influenza, 32 of septicemia and bacteremia, 25 of fever of unknown or uncertain cause, and 23 of miscellaneous infectious diseases, such as typhoid fever, paratyphoid fever and tularemia. The levels determined in cases of the pneumonias, although belonging in this classification, were compiled separately because of their great number. The cases of localized infections included 91 of acute infections of the upper respiratory tract, 17 of empyema and pleurisy, 26 of infections of the eye and ear, including the mastoid, 72 of cutaneous and subcutaneous abscesses, 16 of carbuncles, 43 of cellulitis, 41 of infections of the genitourinary tract, 25 of infections of the pelvic region, 20 of acute gastroenteritis and enterocolitis, and 11 of miscellaneous infections. A glance at the figure shows that a great number of these infections were accompanied by a lowered blood diastase level. In general, there were no significant differences between the diastase levels in cases of generalized infections and those in cases of localized infections. It should always be borne in mind, in mentioning infections that secondarily involve the liver, that the same factor may affect the kidneys too, functionally or morphologically. The resultant disturbance, if severe enough, may lead to a retention of circulating diastase sufficient to obscure the depression caused by the hepatic involvement.

13 Katsch, G. Diastase im Blut, *Munchen med Wchnschr* 81 505, 1934

Pneumonia—In a previous note from this laboratory,^{4b} it was reported that low diastase levels were usually found in cases of pneumonia. Figure 3 B, which confirms this preliminary report, is a compilation of the diastase levels determined in 141 cases of pneumonia, with the infection preponderantly bronchial in 105 and lobar in 36. The diastase levels associated with the pneumonias were generally lower than those with any other type of infection, and those associated with the lobar type showed the greater decrease. Usually, the more toxic the infection, the lower the diastase level.

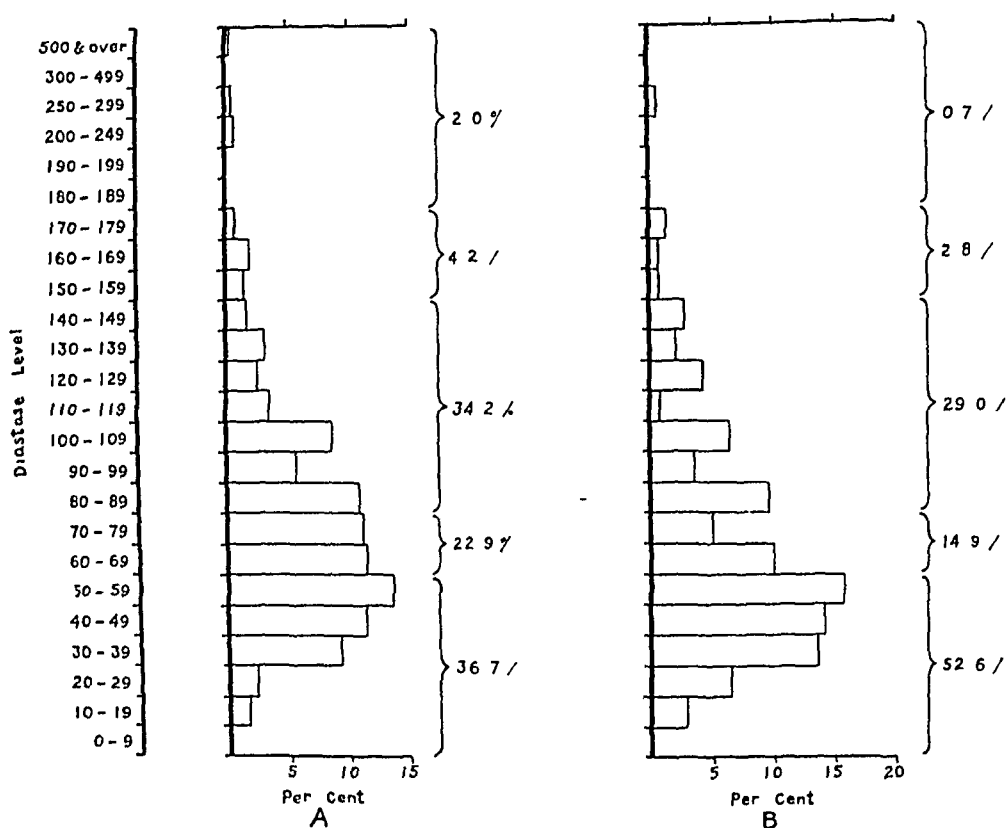


Fig 3—Blood diastase levels in (A) 587 cases of generalized and localized infections and (B) 141 cases of pneumonia

Cardiac Decompensation—We have been able to find but one report on the blood diastase levels in cases of cardiac diseases, and this gave bizarre and unexplainable levels for unspecified types of cardiac and cardiorenal diseases.¹⁴ Our observations indicated that the blood diastase level in patients with cardiac disease is closely related to the extent of decompensation and the accompanying enlargement of the liver. Histologically, one can discern the various stages of central lobular change due to chronic passive congestion. The resulting

14 Rowntree, L. G., Marshall, E. K., Jr., and Baetjer, W. A. Further Studies of Renal Function in Renal, Cardiorenal and Cardiac Diseases, *Arch Int Med* 15: 543 (April) 1915

depletion of the functional liver reserve is reflected in the diastase levels in patients with such disease. A comparison of *A* and *B* in figure 4 shows that in 130 patients with cardiac decompensation the diastase levels were usually depressed to a variable extent, while in 57 patients with cardiac disease in which there was no evidence of decompensation the diastase levels were about the same as in "hospital normals".¹

Diabetes Mellitus—The presumptive role of diastase in hepatic glycogenolysis led several investigators to inquire into the change of blood diastase levels associated with diabetes mellitus. Some workers

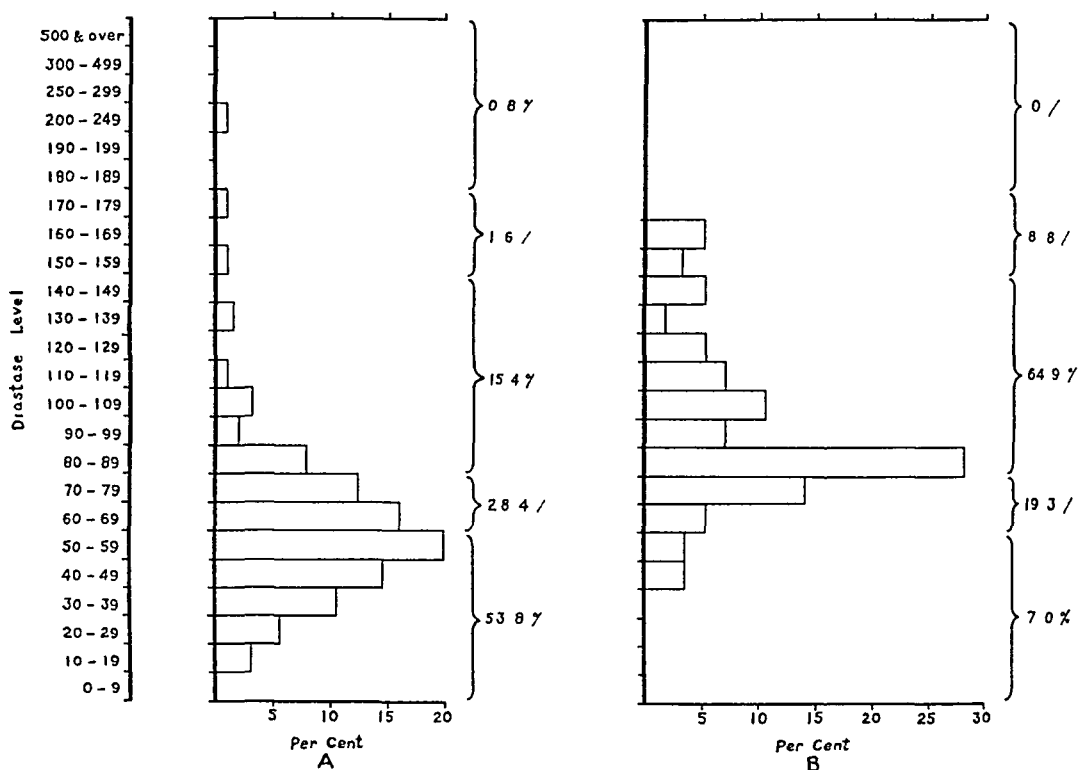


Fig 4—Blood diastase levels in (*A*) 130 cases of cardiac decompensation, and (*B*) 57 cases of cardiac disease without decompensation

observed a decrease in the diastatic activity of the blood or of the urine or of both in patients with diabetes mellitus¹⁵. Other observers¹⁶ found

¹⁵ Kaufman, M. Sur le pouvoir saccharissant du sang et des tissus chez les chiens diabetiques, *Compt rend Soc de biol* **44** 130, 1894. Rosenthal, A. Zur Frage der Ausscheidung von diastatischem Ferment im Urin, *Deutsche med Wchnschr* **37** 923, 1911. Marino, E. Ueber die diagnostische Bedeutung der Diastaseausscheidung im Harn, *Deutsches Arch f klin Med* **103** 325, 1911. Corbett, D. The Quantitative Estimation of Amylolytic Ferments in the Urine as a Measure of Certain Pathological Conditions, *Quart J Med* **6** 351, 1913. Lewis, D S, and Mason, F H. The Diastatic Ferments of the Blood, *J Biol Chem* **44** 455, 1920. Schmerel, F. Ueber die verminderte Diastasewirkung des

virtually normal values in patients with diabetes, while still others¹⁷ obtained increases. Attempts to discover a quantitative relationship between the glycemic level and the diastatic activity of the blood were fruitless.

In figures 5 and 6 are presented the diastase levels for 736 hospitalized patients with diabetes. The classification of patients according to the severity of the diabetes is based on sugar tolerance tests and general clinical considerations. We are aware that such a classification is not objectively precise, yet we have used it because of the lack of a more adequate scale. A revaluation of his diabetic condition was made each time a patient was readmitted to the hospital. The charts show that as compared with normal persons there is a tendency in the patient with diabetes for the diastase to fall to the low normal or subnormal range. On the whole, the more severe the diabetes, the lower the diastatic activity of the blood. Thus, 74.1 per cent of the 89 patients with severe diabetes and all of the 16 comatose patients had blood diastase levels below 60.

The role assumed by the liver in diabetes mellitus is far greater than a histologic examination of the organ would suggest. While such changes as glycogen depletion and fatty infiltration can be demonstrated,¹⁸ other chemical changes cannot be observed histologically. In

Harns bei Nierenerkrankungen und beim Diabetes, *Biochem Ztschr* **208**:415, 1929. Ottenstein, B. Untersuchungen über den Gehalt der Haut und des Blutes an diastatischem Ferment und dessen biochemische Bedeutung bei Hautkrankheiten, *ibid* **240**:328, 1931. Branisteanu, D., and Boutroux, A. Contribution à l'étude de l'élimination de l'amylase urinaire dans divers cas normaux et pathologiques, *Arch d mal de l'app digestif* **23**:746, 1933.

16 Benczur, J. V. Beitrag zur klinischen Verwertbarkeit der Diastasemenge in Blutserum und Urin, *Wien klin Wchnschr* **23**:890, 1910. Milne, L. S., and Peters, H. Observations of the Glycolytic Power of the Blood and Tissues in Normal and Diabetic Conditions, *J Research* **26**:415, 1912. DeNiord, H. H., and Schreiner, B. F. Diastatic Activity of the Blood in Cancer, Syphilis and Diabetes, *Arch Int Med* **23**:484 (April) 1919. Cameron, G. A Comparison of Dodd's and Sladden's Methods for Estimating Urinary Diastase, *J Metab Research* **3**:753, 1923. Brill, I. C. Studies in the Diastatic Activity of the Blood, with a Consideration of Its Value in Clinical Diagnosis, *Arch Int Med* **34**:542 (Oct) 1924. von Strasser. Untersuchungen über das diastatische Ferment im Blute, *Deutsches Arch f klin Med* **151**:110, 1926. Nørby, G. The Amylase Concentration in the Serum of Diabetics, *Acta med Scandinav*, 1936, supp 78, p 933. Stocks^{9a} Fricker^{9c}.

17 Myers, V. C., and Killian, J. A. Studies on Animal Diastases. I. The Increased Diastatic Activity of the Blood in Diabetes and Nephritis, *J Biol Chem* **29**:179, 1917. Reid, E., and Myers, V. C. Studies on Animal Diastases. IV. The Effect of Insulin on the Diastatic Activity of the Blood in Diabetes, *ibid* **99**:607, 1933.

18 Joslin, E. P. The Treatment of Diabetes Mellitus, ed 6, Philadelphia, Lea & Febiger, 1937, p 166. Warren, S. The Pathology of Diabetes Mellitus, *ibid*, 1938.

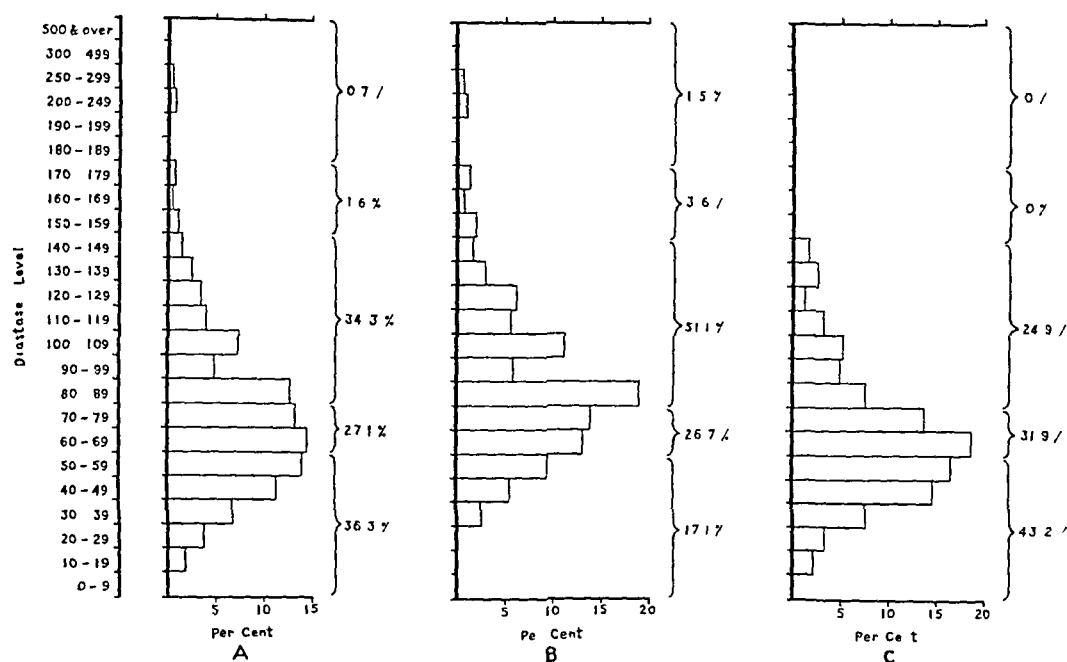


Fig 5—Blood diastase levels in (A) 736 cases of all types of diabetes mellitus, (B) 335 cases of mild diabetes mellitus and (C) 296 cases of moderate diabetes mellitus

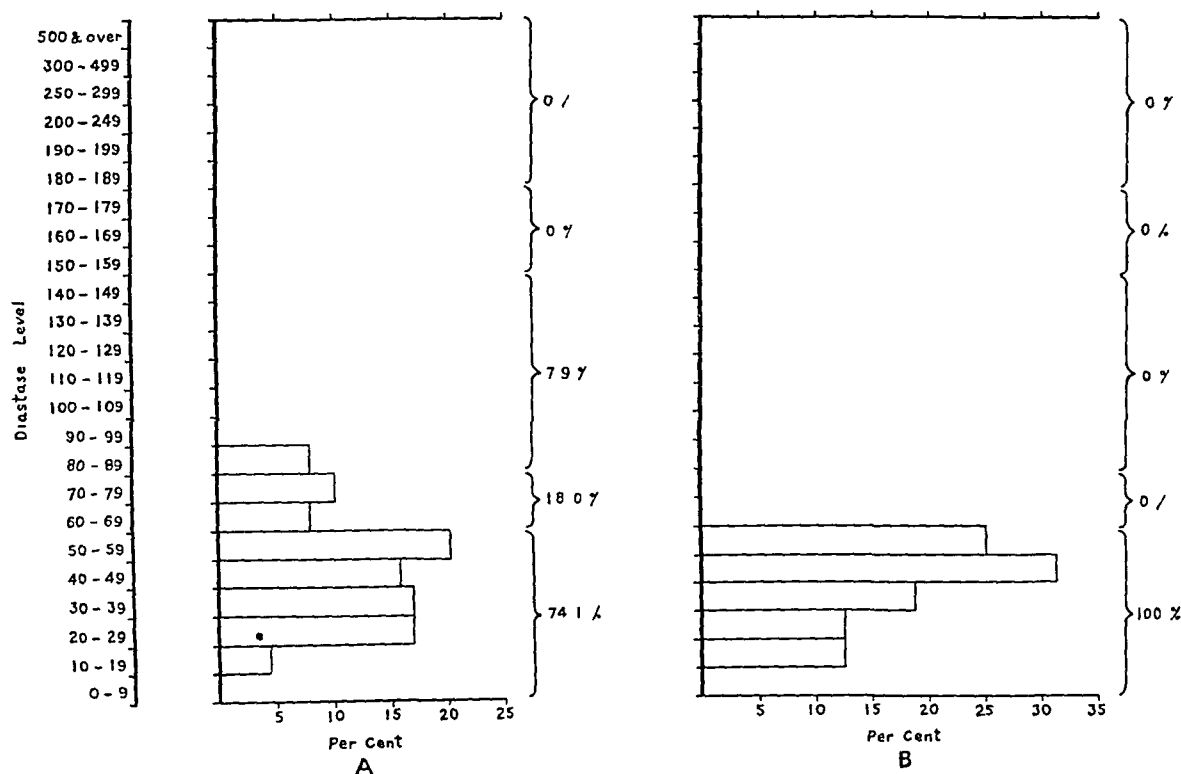


Fig 6—Blood diastase levels in (A) 89 cases of severe diabetes mellitus and (B) 16 cases of diabetic coma

our opinion the aforementioned statistics indicate that impaired hepatic function is a significant factor in diabetes. It is even possible that the liver may play a dominant role in this disease.

Toxemias of Pregnancy—In figure 7 *A* are presented the diastase levels determined in 13 cases of preeclampsia, 3 cases of eclampsia and 8 of vomiting of pregnancy. The chart reveals a tendency in the direction of subnormal diastase levels, but it may also be observed that in the majority of the cases the diastase is still within the normal range. The subnormal diastase values we ascribe to changes known to occur in the liver, i. e., fatty degeneration, hyperemia, hemorrhage, cloudy

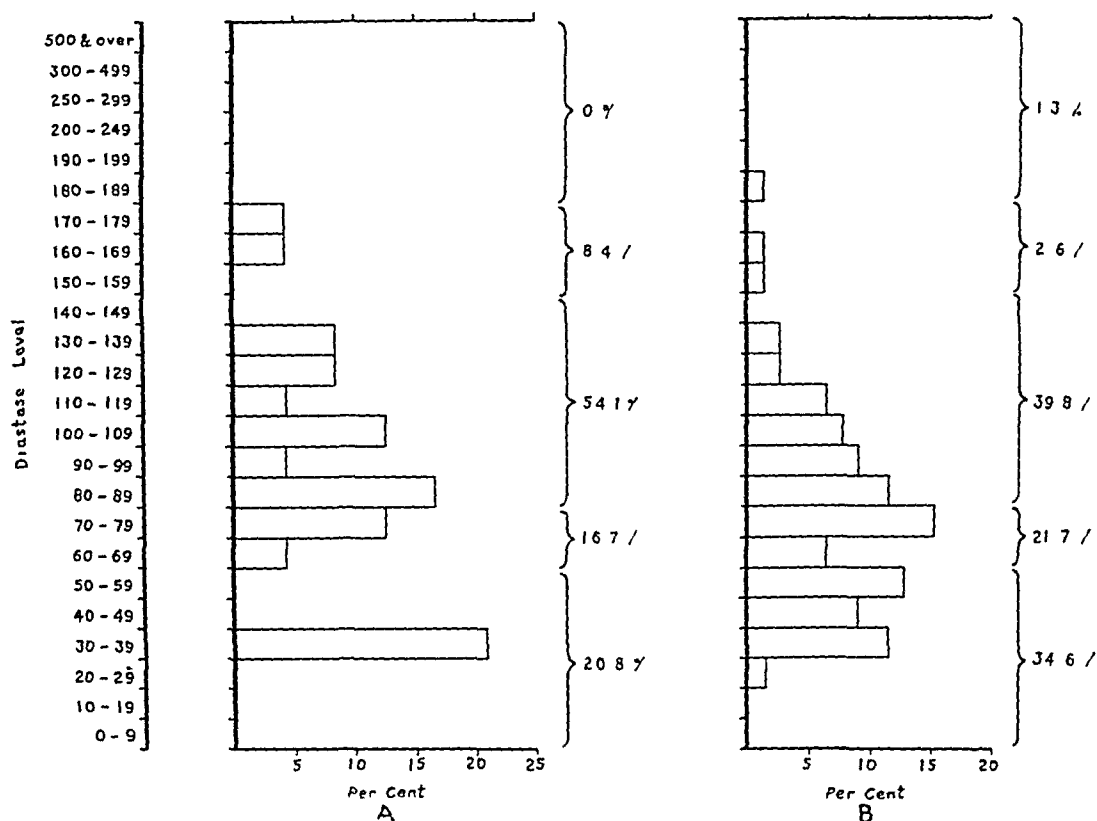


Fig 7—Blood diastase levels in (A) 24 cases of toxemia of pregnancy and (B) 78 cases of thyrotoxicosis

swelling and peripheral lobular necrosis¹⁹. No doubt in many cases in which the blood diastase is within the normal range, estimation of the urine diastase would reveal retention due to renal impairment, known to be present in such toxemias. This would tend to cover up the low level of the blood diastase caused by impaired hepatic function. We have ascertained in a few cases the existence of such a combination of factors, so that we find it necessary to determine both blood and urine diastase in cases of toxemia of pregnancy.

¹⁹ Curtis, A. H. *Obstetrics and Gynecology*, Philadelphia, W. B. Saunders Company, 1933, vol. 1. Katsch¹³

Drug Poisoning—Our records included 11 cases of acute drug poisoning and 8 cases of acute alcoholism. The former subgroup included 3 cases of poisoning with barbiturates, 2 with carbon monoxide and 1 each with chloroform, morphine, acetanilid, compound solution of cresol, carbon tetrachloride and arsenic. Of the 11 cases, in 7 the diastase levels were below 60, and in the remaining 4 (2 cases of barbiturate, 1 of morphine and 1 of acetanilid poisoning) the levels ranged between 70 and 90. Of the cases of acute alcoholism, in 4 the diastase levels were below 60 and in 4 they ranged between 60 and 80. The impairment of hepatic function is reflected in the low diastase values in the majority of these cases of drug poisoning.

Burns—While recognizable pathologic changes in the liver are not usually found in cases of burns, it is hardly possible for the liver to escape the effects of the variable degrees of toxemia that, as a rule, accompanies these conditions. Our records included 22 cases of second and third degree burns. In general, the more severe the burn, the greater the drop in the diastase level. The levels determined in all 8 cases of severe third degree burns fell in the range below 60. Of the remaining 14 cases, in 7 the diastase levels were below 60, in 4 they ranged between 60 and 80 and in 3 they were above 80.

Hyperthyroidism—In previous reports from this laboratory²⁰ it was shown that increased thyroid activity is accompanied by a decrease in the diastatic activity of the blood. This was attributed to the involvement of the liver that usually accompanies thyrotoxicosis. This involvement is manifested clinically by the occasional appearance of jaundice, physiologically by impairment of function as measured by different liver function tests, experimentally by evidence of hepatic dysfunction after administration of thyroid and morphologically by patchy chronic parenchymatous interlobular hepatitis, occasionally with areas of focal necrosis.²¹ Figure 7 *B* shows the diastase levels determined in 78 cases of thyrotoxicosis, including a number of cases more completely studied before.^{20a} In the majority of the cases the patients presented low values at the time of admission to the hospital. While our chart does not include subsequent determinations, our observations in general support the conviction that the diastase level in the same person varies inversely with the degree of toxicity.

Effect of Anesthesia—There have been a few reports on the effect of anesthesia on the blood diastase. On the whole, little effect is

20 Bartlett, W., Jr. (a) Effects upon Blood Amylase of Variations in Thyroid Activity, *Proc Soc Exper Biol & Med* **36** 843, 1937, (b) Variations of Blood Amylase with Thyroid Activity, *Tr Am A Study Goiter*, 1938, p. 494.

21 Waller, C. V. Hepatic Pathology in Exophthalmic Goiter, *Ann Int Med* **7** 543, 1933. Bartlett, W., Jr. The Role of the Liver in Thyrotoxicosis, *Surgery* **3** 261, 1938.

obtained with any type of anesthesia, with the exception of chloroform anesthesia. Ether anesthesia resulted in variable changes in the diastase level.²² Of great interest is the effect on blood diastase of chloroform which exerts a destructive effect on the parenchyma of the liver.²³ All investigators obtained unmistakable lowering of the blood diastase after the administration of chloroform.²⁴ It was also demonstrated that the decrease in diastatic activity was proportional to the length of anesthesia and especially to the amount of liver tissue damaged. Decreases, however, were observed even when lesions could not be demonstrated in the liver.^{23b}

Our clinical material on the effect of anesthesia does not lend itself to analysis. First, we do not use chloroform anesthesia in this hospital. Second, the possible effect of anesthesia cannot be divorced from the effect of the operative procedure. The foregoing observations, however, lead us to assume that, with the exception of chloroform anesthesia, the usual forms of clinical anesthesia effect little change in the level of blood diastase.

Effect of Surgical Operations—Probably no organ requires as much ministrations in the preoperative and postoperative management of surgical patients as does the liver. Active measures are generally taken to preserve or to improve the functional capacity of that organ whenever major operative measures are contemplated. Analysis of the diastase levels determined in a group of selected surgical cases shows that, in spite of these efforts, the liver is appreciably affected by major surgical procedures. Figure 8 (*A* and *B*) represents the preoperative and postoperative diastase determinations in 287 cases in which before operation there was no recognizable evidence of direct or indirect hepatic damage. In these cases after the patients were subjected to major operative procedures directed to tissues or organs other than the biliary tract, diastase determinations were performed a few as early as the day of operation and some as late as ten days after operation. In the group as a whole

22 (a) Watanabe, C. K. Studies on Animal Diastases, *Am J Physiol* **45** 30, 1917. (b) Davis, L. H., and Ross, E. L. The Sources of Diastases of the Blood, *ibid* **56** 22, 1921. (c) Karsner, H. T., Koeckert, H. L., and Wahl, S. A. The Diastatic Activity of the Blood in Experimental Hyperglycemia, *J Exper Med* **34** 349, 1921. (d) Reid, C., and Naravana, B. Studies in Blood Diastase. Factors Which Cause Variations in the Amount of Diastase in the Blood, *Quart J Exper Physiol* **20** 305, 1930. (e) Foged, J. The Clinical Significance of Diastasia. II. Postoperative Diastasia, *Acta chir Scandinav* **69** 543, 1931. (f) Zucker, Newburger and Berg.^{10a}

23 (a) Flagg, P. J. The Art of Anesthesia, ed 2, Philadelphia, J. B. Lippincott Company, 1919. (b) Cajori, F. A., and Vars, H. M. The Effect of Chloroform Anesthesia on Serum Amylase and Liver Esterase, *Am J Physiol* **124** 149, 1938.

24 Carlson, A. J., and Luckhardt, A. B. On the Diastases in the Blood and the Body Fluids, *Am J Physiol* **23** 148, 1908. Zucker, Newburger and Berg.^{10a} Davis and Ross.^{22b} Cajori and Vars.^{23b}

there was a tendency of the diastase level to fall to subnormal values after operation. The greatest decreases were observed on the third and fourth postoperative days, after which there was a tendency to return to the normal range. The few patients showing postoperative diastase levels above normal may reflect a certain degree of renal damage.

Other Conditions Affecting the Liver—It is difficult to draw the line between involvement and noninvolvement of the liver in certain conditions, particularly when such ill defined criteria as functional factors are considered. For example, certain extensive traumas, such as

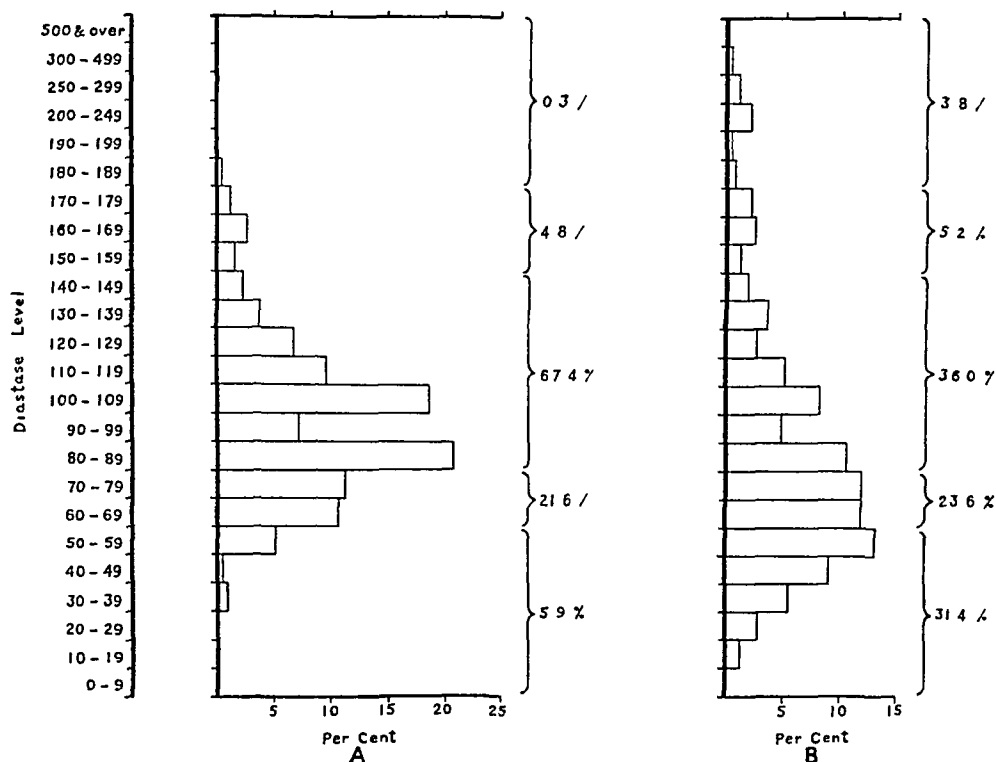


Fig 8—Blood diastase levels in 287 cases in which major operations were performed. *A*, preoperative determinations, *B*, postoperative determinations.

compound fractures and multiple large contusions or hematomas, are probably not without effect on the liver. Certain prolonged debilitating illnesses undoubtedly are to be considered as factors that may cause some hepatic damage. These problematic factors do not lend themselves well to statistical analysis.

CONCLUSIONS

1 A statistical study of considerable clinical material confirms the view previously advanced from this laboratory that subnormal diastase levels are indicative of impaired hepatic function.

2 A decrease in blood diastase on repeated determination is especially significant.

CLINICAL STUDIES ON BLOOD DIASTASE

II SIGNIFICANCE OF INCREASED BLOOD DIASTASE

CARL J HEIFETZ, M D

J G PROBSTEIN, M D

AND

S H GRAY, M D

ST LOUIS

In another report from this laboratory ¹ the normal range of diastatic activity of the blood was established, based on determinations by the analytic technic of Somogyi ² It was shown that this range lies between 80 and 150 and that the ranges between 60 and 80 and between 150 and 180 are on the borderline of normal Diastase values below 60 and above 200 are considered definitely abnormal The present report is concerned with pathologic conditions which in general are associated with abnormal increases in the level of the blood diastase Those associated with subnormal levels were discussed in a separate report "

The patients whose cases are included in this study were admitted between 1933 and 1938 to the Jewish Hospital, a general hospital for patients with acute conditions, excluding contagious and mental diseases Since only one determination was made in the majority of cases, we have disregarded repeated determinations in the same cases and have selected only the initial values for our compilation Because in some of our cases, particularly those in which there were the greatest changes of blood diastase from the normal, a number of determinations were made, the statistics do not necessarily indicate values for the maximum change Cases in which the patients were readmitted to the hospital were dealt with as new cases

Aided by the David May-Florence G May Fund

From the laboratory and the Department of Surgery, Jewish Hospital, and the Department of Surgery, Washington University School of Medicine

1 Somogyi, M Diastatic Activity of Human Blood, Arch Int Med **67** 665 (March) 1941 Somogyi states "The terms diastase and amylase are often used interchangeably I prefer the term diastase to denote the enzyme dealt with in this study, an enzyme which is not only an amylase, but a glycogenase and a dextrinase as well "

2 Somogyi, M Micromethods for the Estimation of Diastase, J Biol Chem **125** 399, 1938

3 Gray, S H , Probstein, J G , and Heifetz, C J Clinical Studies on Blood Diastase I Low Blood Diastase as an Index of Impaired Hepatic Function Arch Int Med , this issue, p 805

Abnormally high levels of blood diastase have long been observed, since they are amenable to detection by means of rather crude analytic methods. Although such levels were generally considered as resulting exclusively from disease of the pancreas,⁴ it is now known that elevated values for blood diastase may also be obtained in cases of impaired renal function and of some acute diseases of the salivary gland.

PANCREATIC DISEASE

An increase in the blood diastase in cases of acute pancreatic disorders has been frequently noted. Determination of the diastase level was first hailed as a test for pancreatic function, and some authors still harbor the conviction that any pathologic condition of pancreatic origin is associated with an elevation of the diastase level. It has been shown by animal experimentation that all pancreatic lesions, whether the result of trauma, ligation of the duct, acute pancreatitis or partial pancreatectomy, cause rises in blood diastase which persist for only a few days, then the diastase levels tend to revert to normal. Hence, changes in blood diastase of pancreatic origin are usually temporary. This is precisely the experience in cases of diseases of the human pancreas. Only the acute diseases of the pancreas produce notable changes in the blood diastase. Chronic lesions, such as benign and malignant tumors and chronic pancreatitis, either have no effect at all⁵ or produce an increase in diastase only by sudden acute involvement of previously unaffected pancreatic tissue.⁶ For example, a carcinoma of the pancreas might be present in its early stages without causing any change in the blood diastase. As the lesion spread, there might be fairly rapid occlusion of a pancreatic duct or artery, resulting in a sudden elevation of the diastase level which would be followed by a return to the previous level. Further spread of the lesion might even cause sudden inflammatory involvement of adjacent normal

4 Unger, E, and Heuss, H. Internistisches Korreferat zur Chirurgie des Pankreas, *Arch f klin Chir* **148** 71, 1927. Walzel, P. Zur Diagnose und Therapie der akuten Pankreasnekrose, *Beitr z klin Chir* **147** 1, 1929. Bernhard. Die Bedeutung der Lipase- und Diastasebestimmungen für die chirurgischen Eingriffe an den Gallenwegen, *Arch f klin Chir* **173** 14, 1932. Peterson, L. Einige Worte über die Diagnose und Behandlung der akuten Pankreaskrankheiten, *Zentralbl f Chir* **61** 133, 1934.

5 (a) Cameron, G. A Comparison of Dodd's and Sladden's Methods for Estimating Urinary Diastase, *J Metab Research* **3** 753, 1923. (b) Brill, I. C. Studies in the Diastatic Activity of the Blood, with a Consideration of Its Value in Clinical Diagnosis, *Arch Int Med* **34** 542 (Oct) 1924.

6 Wakefield, E, McCaughan, J, and McVicar, C. Amylase in Blood in Subacute and Chronic Pancreatic Diseases, *Arch Int Med* **45** 473 (March) 1930. McCaughan, J. M. The Value of Estimations of the Amylase of the Blood in the Diagnosis of Suspected Pancreatic Disease, *Surg, Gynec & Obst* **59** 598, 1934. Clasen, A. C., Johnstone, P. N., and Orr, T. G. Blood Amylase in Experimental Pancreatitis, *ibid* **59** 756, 1934. Foged, J. The Diagnostic Value of Urine Diastase, *Am J Surg* **27** 439, 1935.

pancreatic tissue, resulting in another temporary rise in the diastase level. The low grade inflammatory lesions vaguely denoted as chronic pancreatitis would, according to this concept, produce no changes in the blood diastase, and such has been the experience of clinicians.

The use of the term "acute pancreatic lesions" is tantamount to specifying acute pancreatitis. In no other condition has the diastase determination been of such clinical value. Whether the lesion is of the edematous, hemorrhagic, suppurative or necrotic type, any of which may be different stages of the same process, there is always an elevation of the diastase during the acute stage of the disease. This rise occurs almost simultaneously with the onset of symptoms. In the transient type of lesion,⁷ which we believe by far the most common, the elevation of the diastase may last no longer than thirty-six to forty-eight hours, however, it may persist for a number of days, presumably in the more severe and more progressive lesions. The mechanism responsible for the rise associated with acute pancreatitis has been discussed previously.^{7e}

The early and repeated use of the diastase test during such emergencies has in our experience uncovered cases of transient acute pancreatitis which would have otherwise masqueraded under other diagnoses. We have previously expressed the view that the role of the pancreas in the production of pain in the upper part of the abdomen has frequently been overlooked.^{7e} Since all cases of acute pancreatitis are associated with an elevated diastase level early during the illness, it is logical to assume that if normal diastase values are obtained during the height of an attack, the pancreas may be excluded from consideration in the problem of differential diagnosis. Isolated reports of cases of acute pancreatitis in which the diastase values are normal probably reflect mistaken diagnoses or tardy diastase determinations. The last assumption finds support in a few of our own observations. We feel that repeated determinations of the diastase in the blood and urine of patients with acute pain in the upper part of the abdomen will reveal that a surprisingly large number of them have transient acute pancreatitis.

Figure 1 is a graphic representation of the diastase levels of 36 patients with acute pancreatitis at the time they were admitted to the Jewish Hospital. It may be noted that the values were greatly elevated above the normal level, the majority being well above 500 and that in 1 case being as high as 3,600. It may be mentioned here that urine diastase values ran as high as 25,000. As has been stated before, the

7 (a) Zoepffel, H. Das akute Pankreasodem, eine Vorstufe der akuten Pankreasnekrose, *Deutsche Ztschr f Chir* **175** 301, 1922. (b) Archibald, L. Acute Edema of the Pancreas, *Ann Surg* **90** 803, 1929. (c) Leveuf, J. Les pancreatites oedemateuses, *Rev crit de path et de therap* **2** 373, 1931. (d) Elman, R. The Variations of Blood Amylase During Acute Transient Disease of the Pancreas, *Ann Surg* **105** 379, 1937. (e) Gray, S. H., Probst, J. G., and Heifetz, C. J. Transient Acute Pancreatitis, *ibid* **108** 1029, 1938.

values on this chart do not necessarily represent the highest level in each case. For example, in 1 case in which there was an initial blood diastase level of 189, a maximum level of 610 developed later. The former level is included in the chart, while the latter is not. In 2 other cases in which the blood diastase levels were 170 and 192, respectively, the determinations were undoubtedly made late during the attack, for the urine diastase

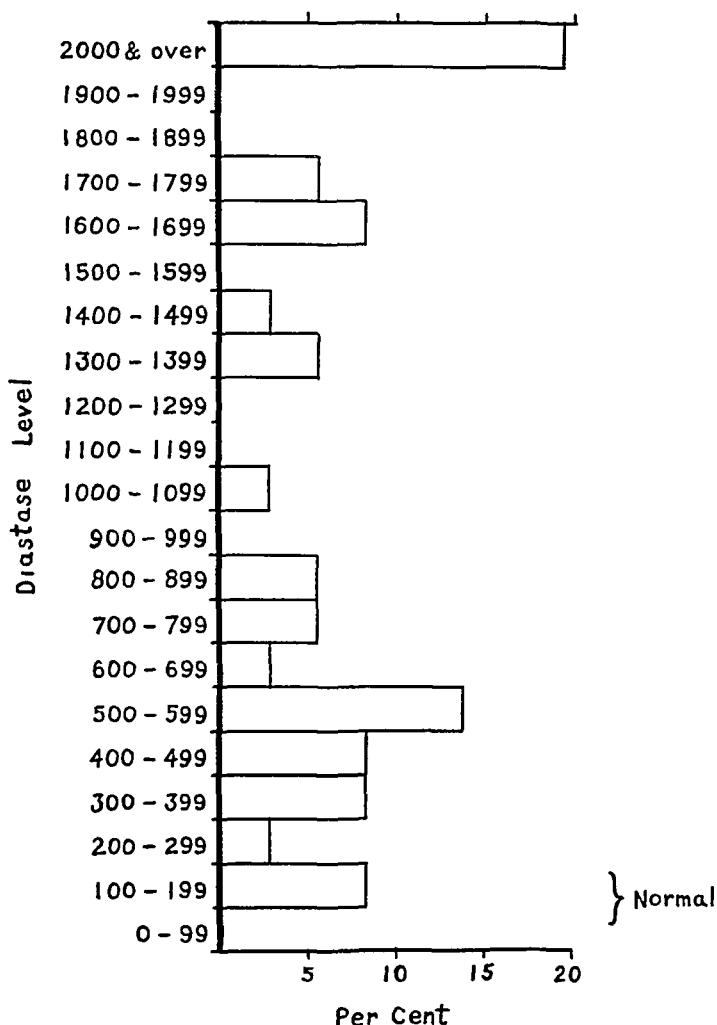


Fig 1—Blood diastase levels in 36 cases of acute pancreatitis

levels determined at the same time were 1,426 and 1,600, respectively, and shortly thereafter the levels in the urine dropped to normal. The lag of change in urine diastase by several hours can sometimes be utilized to help establish a diagnosis of acute pancreatitis, if the patient is seen during the subsidence of an attack.

After the height of an attack, a gradual or precipitous drop of the blood diastase to a normal or even a subnormal level could always be observed. Since in many cases acute pancreatitis is associated with disease of the biliary tract, the drop to a subnormal level can be ascribed

to the latter³ In 2 of our cases the disease was proved at autopsy to be of the necrotic type, in the remainder 10 of which were included in a previous report,^{7e} it fell in the group of transient pancreatitis Since it is not our custom to operate on patients with such a condition during the acute attack, the exact nature of the lesions was not disclosed It is probable that the disease in the majority of cases would have gone unrecognized if diastase determinations had not been performed Our hospital records show few cases of diagnosed acute pancreatitis prior to the introduction of diastase determinations in our laboratory, whereas in the last few years this condition has been encountered with increasing frequency

PERFORATING PEPTIC ULCER

In a previous report from this laboratory⁸ it was shown that when a peptic ulcer penetrates into or near the pancreas there is a tendency for the diastase to rise slightly above the normal level, but not nearly as high as in cases of acute pancreatitis With perforations occurring elsewhere no such rises were obtained The elevations associated with posterior perforations are, therefore, due to involvement of the pancreas The relatively small rise is commensurate with the small localized nature of the process and the ability of the superficially necrotic tissue to drain into the stomach or duodenum

The task of differentiating this relatively uncommon type of perforation from acute pancreatitis is not an easy one Although the diastase level is generally considerably lower in cases of the former, there is no sharp line of demarcation between the levels associated with the one and with the other At the same time the differentiation is of the utmost clinical importance, since the treatment of perforations is almost always surgical, while we consider operative measures contraindicated during the acute stages of acute pancreatitis^{7e} Here, clinical judgment, as it should be, is the paramount determining factor No such problem, of course, arises in cases of anterior perforations, which constitute by far the majority⁹

DISEASES OF THE SALIVARY GLANDS

Elevated diastase values have been found in cases of acute infection of the parotid gland, including some cases of mumps¹⁰ In a small series

8 Probstein, J G, Wheeler, P A, and Gray, S H Perforated Peptic Ulcer Its Differentiation from Acute Pancreatitis by Blood Diastase Determinations, *J Lab & Clin Med* **24** 449 (Feb) 1939

9 Walton, A J Surgery of Stomach and Duodenum, in Nelson New Loose-Leaf Surgery, New York, Thomas Nelson & Sons, 1937, vol 5, p 47

10 (a) Dunlop, G A The Diastatic Index in Acute Parotitis, *Lancet* **2** 183, 1933 (b) Branisteanu, D, and Boutroux, A Contribution a l'étude de l'élimination de l'amylase urinaire dans divers cas normaux et pathologiques, *Arch d mal de l'app digestif* **23** 746, 1933

of cases of mumps at the St. Louis City Isolation Hospital, no elevation of the blood diastase was found. Our own observations have been confined to only a few cases of disease of the salivary glands. Appreciable increases in the diastase level were observed in cases of calculous obstruction to the salivary duct and in cases of suppurative lesions.

The possibility of confusing acute diseases of the salivary glands with those of the pancreas is remote, since a pathologic condition of the salivary gland is relatively easy to recognize.

RENAL DISEASES

The blood diastase level may be elevated in still another condition, namely, the accumulation of diastase in the blood due to failure of renal excretion. The exact renal mechanism of diastase excretion is not known. It is known, however, that impaired renal function is usually associated with retention of diastase in the blood¹¹ and diminished excretion in the urine¹².

The ratio of urine diastase to blood diastase has been suggested as an index of renal function¹³. It was pointed out in a preliminary report

11 (a) Stocks, P. The Quantitative Determination of Amylase in Blood Serum and Urine as an Aid to Diagnosis, *Quart J Med* **9** 216, 1916. (b) Myers, C. V., and Killian, J. A. Studies on Animal Diastases. I. The Increased Diastatic Activity of the Blood in Diabetes and Nephritis, *J Biol Chem* **29** 179, 1917. (c) Harrison, G. A., and Lawrence, R. D. Diastase in Blood and Urine as a Measure of Renal Efficiency, *Lancet* **1** 169, 1923. (d) Stafford, D. D., and Addis, T. Diastase Determinations in Urine and Blood as a Method for the Measurement of the Functional Capacity of the Kidney, *Quart J Med* **17** 151, 1924. (e) Gray, S. H., and Somogyi, M. Relationship Between Blood Amylase and Urinary Amylase in Man, *Proc Soc Exper Biol & Med* **36** 253, 1937. (f) Brill^{5b}.

12 (a) Hirata, G. Beitrag zur Verhalten der Diastase im Blut und im Urin beim Kaninchen, *Biochem Ztschr* **28** 23, 1910. (b) Rosenthal, A. Zur Frage der Ausscheidung von diastatischem Ferment im Urin, *Deutsche med Wchnschr* **37** 923, 1911. (c) Marino, E. Ueber die diagnostische Bedeutung der Diastaseausscheidung im Harn, *Deutsches Arch f klin Med* **103** 325, 1911. (d) Corbett, D. The Quantitative Estimation of Amylolytic Ferments in the Urine as a Measure of Certain Pathological Conditions, *Quart J Med* **6** 351, 1913. (e) Rowntree, L. G., Marshall, E. K., Jr., and Baetjer, W. A. Further Studies of Renal Function in Renal, Cardiorenal and Cardiac Diseases, *Arch Int Med* **15** 543 (April) 1915. (f) Wallis, R. L. M. Demonstration on the Diastase Content of the Urine in Toxemias of Pregnancy, *Brit M J* **2** 273, 1920. (g) Sladden, A. F. Some Observations on the Diastase Reaction of the Urine, *Lancet* **2** 68, 1922. (h) Schmerel, F. Ueber die verminderte Diastasewirkung des Harns bei Nierenerkrankungen und beim Diabetes, *Biochem Ztschr* **208** 415, 1929. (i) Cameron^{5a}. (j) Branisteanu and Boutroux^{10b}. (k) Stocks^{11a}. (l) Myers and Killian^{11b}. (m) Harrison and Lawrence^{11c}. (n) Stafford and Addis^{11d}. (o) Gray and Somogyi^{11e}.

13 Lavaglio, R. L'indice diastatico del sangue e delle urine in un gruppo di epatopazienti, *Policlinico (sez med)* **35** 221, 1928. Stafford and Addis^{11d}. Gray and Somogyi^{11e}.

from our laboratory^{11c} that under normal conditions there is a well defined relationship between the diastase level of the blood and that of the urine. This relationship is such that the ratio of the amount of diastase excreted in the urine per hour to the diastatic activity of the blood is always above unity. When renal retention is present, this ratio falls to unity or below unity. The more severe the retention, the lower this ratio becomes. At the same time diastase accumulates in the blood and may rise considerably above the normal level. An increase in blood diastase, however, is not always present. For example, the pathologic condition causing the disturbance of renal function may at the same time produce impairment of hepatic function. Since the latter condition tends to lower the blood diastase level, a normal or subnormal blood diastase level may result when both impaired hepatic function and impaired renal function are effective concurrently. Even so, reversal of the urine diastase-blood diastase ratio is present. Thus, several of our cases in which there were subnormal blood diastase values and virtual absence of urine diastase become readily understandable.

It has been suggested that the diminished urinary excretion of diastase associated with renal diseases be employed as a test of renal function.¹⁴ We have found this inaccurate and inapplicable partly because of the wide fluctuations in the diastase content of normal urines and partly because low urine diastase may be simply the sequel of low blood diastase. Thus it is evident that diastase determinations for renal function furnish information only if the blood diastase and urine diastase are estimated simultaneously. Such estimations of diastase in this laboratory have given results roughly paralleling those of other renal function tests.

It is likely that the occasional finding of an elevated blood diastase level in an apparently healthy normal person may be due to a slight degree of renal retention which escapes symptomatic and clinical observation. This assumption suggests the advisability of determining the urine diastase-blood diastase ratio whenever moderately elevated blood diastase values are found. In this way early disturbances in renal excretion may be uncovered.

Figure 2 shows the blood diastase levels in 111 cases of renal insufficiency, selected on the basis of clinical and laboratory data. The group comprises cases of acute and chronic glomerulonephritis, idiopathic and toxic nephrosis, suppurative lesions of various types (especially obstructive), nephrosclerosis and the like. In many of the cases there was associated azotemia. Included were 32 cases in which clinical and laboratory data presented evidence of impaired renal function, but in which blood diastase levels were below 200. Unfortunately, the failure to determine

14 Wohlgenuth, J. Experimentelle Beiträge zur Prüfung der Nierenfunktion, *Ztschr. f. Urol.* 5: 801, 1911.

the urine diastase levels in 20 of these cases gave us an incomplete picture of the renal excretion of diastase. However, determinations of urine diastase were made in the other 12 cases in which blood diastase levels were below 200, in 10 of which a reversal of the urine diastase-blood diastase ratio was found. The majority of the diastase levels in our cases of renal insufficiency fell within the range of 200 to 500. It is notable that while in 72.3 per cent of the cases of acute pancreatitis

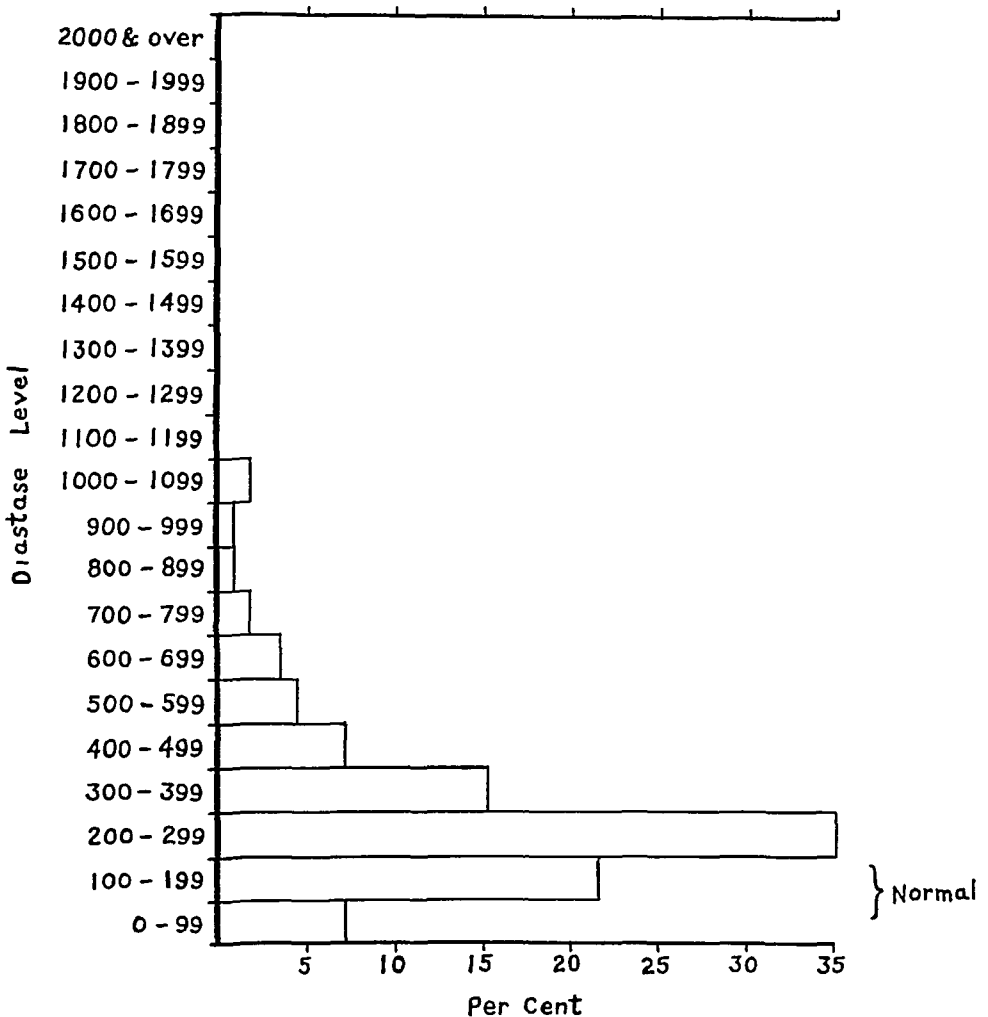


Fig 2—Blood diastase levels in 111 cases of renal insufficiency

the diastase levels were above 500, in only 13.5 per cent of the cases of renal insufficiency were there levels above this figure. In these 15 cases there was renal impairment of the severest degree, and in only 2 were the diastase levels slightly above 1,000. It can be seen, therefore, that the blood diastase in cases of renal diseases seldom attains the height reached in cases of acute pancreatitis.

CONCLUSIONS

1 Elevated blood diastase values are found in cases of acute pancreatitis, perforation of peptic ulcer into or near the pancreas, occlusion of the salivary duct, suppuration of the salivary glands and impairment of renal function

2 When the blood diastase level is elevated to 1,000 or higher, in general it is safe to assume the presence of acute pancreatitis. Rare exceptions are encountered in cases of occlusion of the salivary duct. The clinical picture here will allow differentiation without difficulty.

3 When moderate degrees of elevated blood diastase, e. g., 200 to 1,000, are found, it becomes indispensable to determine the urine diastase-blood diastase ratio. If this ratio is lowered to unity or below unity, the primary cause is deficient renal excretion of diastase. The increase of the diastase level under such circumstances seldom exceeds 500, but in a few cases of exceptionally severe renal insufficiency in a group of 111 cases blood diastase levels as high as 1,000 were observed.

4 Moderate increases in blood diastase also may occur in cases of perforation of posterior peptic ulcer into or near the pancreas. While the increases in these cases rarely approach those found in cases of acute pancreatitis, the differentiation of these two conditions by means of diastase determinations alone is unsafe.

5 Diastase determinations judiciously correlated with clinical observations and other laboratory data offer an important aid to diagnosis.

EFFECT OF EDEMA AND INTEGUMENTARY INFILTRATIONS ON BASAL METABOLISM, ELECTROCARDIOGRAM AND BLOOD CHOLESTEROL

ELI MOSCHCOWITZ, M D

NEW YORK

The most obvious example of a lowering of basal metabolism occurring in an edematous state is witnessed in the so-called nephroses, or better termed "hypoproteinemias." Because of this association, Epstein¹ regarded "nephrosis" as a metabolic disease. Indeed, the remarkable tolerance of patients with such a condition for thyroid preparations seemed to justify this contention. However, with the evolution of the broader concept of the "nephrosis" it soon became apparent that the disease could not be a primary metabolic disorder, because a lowered basal metabolism accompanies most conditions, both renal and extrarenal, in which hypoproteinemia is a prominent finding. In other words, the lowered basal metabolism is a secondary and not a primary phenomenon, and the immediate issue with which this study is concerned is the determination of the factor or factors which cause its depression. This in turn leads to a larger problem, namely, the relation of lowered metabolism to edematous states of the human frame of other than hypoproteinemic origins.

Investigations of the first-named problem have hitherto been few and mostly theoretic. Volhard² dismissed the problem with the remark that whether the low basal metabolic rate is due to increased elimination, inactivation or insufficient absorption of thyroxin is unknown. Platt³ applied himself directly to the solution of the questions propounded by Volhard and, employing the tadpole test on the urine of patients with "nephrosis," found that "beyond doubt nothing approaching the amount of thyroxin administered is being excreted by the patient in an unchanged condition. It is therefore presumed that thyroxin is either being rapidly destroyed in the body or its action is inhibited." Platt also held that

From the Second Medical Service, Mount Sinai Hospital

1 Epstein, A. A. Parenchymatous Nephritis, *J. A. M. A.* **69** 444 (Aug. 11) 1917

2 Volhard, F. Die doppelseitigen hamatogenen Nierenerkrankungen, in von Bergmann, G., and Staehelin, R. *Handbuch der inneren Medizin*, Berlin, Julius Springer, 1931, vol. 6, pt. 2

3 Platt, R. *Quart. J. Med.* **23** 129, 1929

the hypothesis that thyroxin is not absorbed in "nephrosis" can be laid aside, since thyroxin introduced intravenously is as well tolerated as that taken orally. Platt's experiments are vitiated by the assumption that the basal metabolism is controlled by the thyroid secretion alone. The thyroid factor seems also to have been considered as dominant by Wolbach and Blackfan,⁴ who found in 8 cases of "nephrosis" a diminution of colloid in the thyroid gland similar to that found in malnutrition. Eppinger⁵ also found a diffuse parenchymatous damage in the thyroid gland in "water edema," but he did not regard this finding as of much consequence, because the same lesion is found in so many nonedematous states. On the other hand, Barker and Kirk⁶ found no changes in morbid anatomy in the thyroid glands of animals made edematous by plasmapheresis, so that they inferred that the lowered basal metabolism is probably only a protective mechanism similar to that witnessed in inanition and starvation. Fahr⁷ expressed the belief that the lowered basal metabolism in "nephrosis" is produced by a number of factors: (1) the added weight of the water, inclusion of which in the calculation tends to lower the determined metabolism by between 5 to 10 per cent of the total calories, (2) the fact that patients with such conditions eat less than their basal requirements and are therefore in a state of chronic starvation, and (3) the thyroid hormone may be filtered out of the blood in the same manner as the smaller colloidal particles of serum albumin. Epstein and Lande⁸ explained the lowered basal metabolism in "nephrosis" as the result of a defective protein metabolism in this disease and a diminution in the specific dynamic action normally imparted by the products of protein metabolism. After observing 4 patients suffering from diabetes and nephritis with edema, Aub and DuBois⁹ expressed the belief that the diminished metabolism was to be expected in an organism diluted by a large mass of inert fluid. In one child, the basal metabolism may have been further lowered by a restricted diet for a period of two months before the calorimetric observation.

4 Wolbach, S. B., and Blackfan, K. D. Clinical and Pathologic Studies on Nephrosis, *J. A. M. A.* **92** 2134 (June 22) 1929.

5 Eppinger, H. *Zur Pathologie und Therapie der menschlichen Odems*, Berlin, Julius Springer, 1917.

6 Barker, M. H., and Kirk, E. J. Experimental Edema (Nephrosis) in Dogs in Relation to Edema of Renal Origin in Patients, *Arch. Int. Med.* **45** 319 (March) 1930.

7 Fahr, G. *Am. J. M. Sc.* **194** 449, 1937.

8 Epstein, A. A., and Lande, H. Studies on Blood Lipoids. Relation of Cholesterol and Protein Deficiency to Basal Metabolism, *Arch. Int. Med.* **30** 563 (Nov.) 1922.

9 Aub, J., and DuBois, E. F. Respiratory Metabolism in Nephritis, *Arch. Int. Med.* **19** 865, 1917.

This foregoing survey reveals the confusion surrounding the problem and suggests that a host of factors is involved. As the normal basal metabolism is maintained and modified by many factors, a discussion of those pertinent to the problem is essential.

FACTORS PERTINENT TO THE PROBLEM

1 *Weight and Surface Area*—It must be obvious that the increase in weight that arises in "nephrotic" conditions, especially in the form of inert water, must modify basal metabolic readings when the computation is made, as in general practice, according to a weight-surface area formula. The greater the weight and therefore the greater the surface area, the lower the tendency to a lower calorimetric reading. The correction for each person is practically impossible, because the physician is only rarely aware of the basal metabolic rate of the patient before the nephrotic syndrome set in, nevertheless, according to Boothby and Sandiford,¹⁰ who found in 94 cases of obesity that the basal metabolism was within 10 per cent of normal in 81 per cent and within 15 per cent in 95 per cent of the cases, one can estimate that the correction need never be more than 10 per cent or perhaps 15 per cent, a reading which is higher than that found in the average case of "nephrosis." The readings will also not be greatly modified by the fact that in "nephrosis" the increment in weight is water, whereas in ordinary endogenous obesity it is stored fat, because both are comparatively inert as far as influencing the metabolism is concerned.

It may be concluded, therefore, that the increase in weight and surface area in a given case of the nephrotic syndrome may lower the basal metabolic rate to a certain degree, but that these increases are responsible only for a moiety of the lowering.

2 *Undernutrition*—A lowered caloric intake, especially of protein, may unquestionably lower the basal metabolism in a given case of the nephrotic syndrome. This was particularly relevant in former years, when a low protein diet and a corresponding emphasis on a high carbohydrate diet were the fashion. However, I have observed that even with seemingly adequate diets the initial basal metabolism of patients with "nephrosis" is remarkably low, and, moreover, the metabolism is not appreciably influenced by a diet rich in protein, probably for the reason that when the nephrotic syndrome is the result of loss of protein the loss compensates quickly for the excess of intake. One may conclude, therefore, that in an occasional patient with "nephrosis" the basal metabolism may be lowered by a low protein diet and inanition, but this factor is responsible for only a fraction of the lowered basal metabolic rate.

10 Boothby, W. M., and Sandiford, I. *J Biol Chem* **54** 783, 1922

3 *Specific Dynamic Action*—The loss or inadequate formation of protein in the various forms of the nephrotic syndrome in combination with an inadequate intake of protein would suggest that part or all of the loss of calory production may be the result of loss of specific dynamic action, in which protein is by far the most potent element. Studies on the specific dynamic action of protein in "nephrosis" are unfortunately not available, but in a case of aggravated nephrotic syndrome consequent on glomerulonephritis with a consistent basal metabolic rate of between — 30 and — 40 per cent, Dr William Hitzig found the specific dynamic action to be perfectly normal.

4 *Lack of Exercise and Sedentary Life*—As patients with a nephrotic syndrome perforce must lead sedentary lives, the basal metabolism tends to be somewhat lower. To what extent a sedentary existence lowers the metabolism among the multitude of other factors to which the patient is subject it is impossible to calculate, but the probability is strong that the amount is insignificant.

5 *Anemia*—The part played by the secondary anemia that usually accompanies a nephrotic syndrome is also difficult to estimate because of many other complicating factors, for instance, the inactivity of the patient that often accompanies an anemic state. Furthermore, the cause of the anemia in "nephrotic" conditions is not known, nor is it by any means certain that the anemia in "nephrosis" is the result rather than a cause of the lowered basal metabolism. In this connection, the investigations of Bomford¹¹ on the anemia of myxedema are intriguing. He held that the thyroid gland in myxedema plays no part in erythropoiesis and that the anemia in myxedema, unless complicated by a deficiency of iron or liver, is a physiologic adaptation on the part of the erythron to a diminished need of the tissues for oxygen. He observed three types of anemia in association with myxedema. The simple hypochromatic type is the uncomplicated anemia of myxedema. It is considered to be part of a decrease in the size of the erythron, which takes place in hypothyroidism as a physiologic compensation for diminished need of the tissues for oxygen, and to be akin to the anemia which appears in animals exposed to atmospheres with a tension of oxygen greater than normal. This interesting hypothesis may with reason be applied to the mechanism of the development of the anemia in the "nephroses," especially as an "erythiotoxic" substance has not been demonstrated in this clinical group.

6 *Thyroid Activity*—It is only natural, in view of the extraordinary tolerance for thyroid preparations and the benefit derived therefrom, that the lowered basal metabolism in "nephroses" should be viewed as the sole or the major result of diminished thyroid activity. This reasoning

11 Bomford, R. Quart. J. Med. 7 495, 1938.

involves two possible fallacies (a) The basal metabolism is entirely the result of thyroid activity. Actually, as Means¹² demonstrated, it is responsible for only about 40 to 45 per cent of the basal metabolism. There is no valid reason why the depression of the metabolism should be shouldered on the thyroid moiety alone. As I have pointed out, there is no consistent evidence that the secretion of thyroxin is either diminished or inhibited or that thyroxin is poorly absorbed in "nephrotic" conditions. (b) The high tolerance for, and therapeutic benefits of thyroid preparations in, patients with "nephroses" indicate a true deficiency therapy. There is at present no direct evidence that this is so. The fact that thyroid preparations are well borne and efficient in maladies of nonthyroid origin, such as war edema, anorexia nervosa, endogenous obesity and especially the edematous form of scleroderma, indicates that the effect of thyroid preparations in these conditions is not specific but symptomatic. As will be seen, all morbid conditions accompanied by a low basal metabolism, no matter of what origin, are also accompanied by an extraordinary tolerance for thyroid therapy.

These six factors constitute all that have been discussed by previous investigators. There is one other factor that requires serious consideration.

7 The Edema Acting as a Suit of Clothes—Rubner¹³ found that a guinea pig exposed to environmental temperatures below 30 C showed an increased metabolism. Animals protected by a thick fur or a heavy layer of subcutaneous fat do not reveal any change in metabolism when exposed to environmental temperatures between 20 and 30 C. Loewy¹⁴ exposed men to cold air and baths and found that in 47 per cent the metabolism was increased 5 to 91 per cent. He expressed the belief that the rise was the result of conscious or unconscious shivering. Gessler¹⁵ and his associates found that the basal metabolic rate of subjects exposed nude in a cool room increased 10 to 20 per cent as compared with that of normal controls. Hill¹⁶ found that the metabolism was much higher in persons sitting outdoors, especially in cold weather. Hill, Campbell and Gauvain¹⁷ studied the metabolism of children undergoing open air treatment and found in all an increased basal metabolism. Also their metabolism was higher in winter than in summer. According to Deighton,¹⁸ clothing or a coat of hair or fur

12 Means, J. H. Boston M. & S. J. **174** 864, 1916.

13 Rubner, cited by DuBois, E. F. Basal Metabolism in Health and Disease, ed. 2, Philadelphia, Lea & Febiger, 1927.

14 Loewy, A. Arch. f. d. ges. Physiol. **46** 189, 1889.

15 Gessler, H. Deutsches Arch. f. klin. Med. **148** 129 and 140, 1925.

16 Hill, L. The Science of Ventilation and Open Air Treatment, London, His Majesty's Stationery Office, 1919, pt. 1.

17 Hill, L. E., Campbell, J. A., and Gauvain, H. Brit. M. J. **1** 301, 1922.

18 Deighton, T. Physiol. Rev. **13** 427, 1933.

greatly reduces both conduction and convection externally and hence greatly affects basal metabolism. Giaja¹⁹ found an increase in basal metabolism of 78 per cent in geese and 5.4 per cent in hens as the result of the removal of feathers. Benedict²⁰ found that the metabolism was raised 50 per cent in the 'scraggly' pigeon, a bird with a slight feathery covering. Benedict, Landauer and Fox²¹ found that the frizzle hen has a considerably higher metabolism than normally feathered fowls. Its surface temperature is 6 C (10.8 F) higher than that of fowls with a normal plumage. This animal also shows a lack of fatty deposit, an enlarged thyroid gland and an increased heart rate. Boas and Landauer²² reported that hypertrophy of the heart occurs regularly in frizzle fowls. Boas, Landauer and Fox ascribed the cause of the high metabolic rate to the deficiency of plumage which causes a high loss of body heat. The thyroid enlargement they regarded as compensatory. Ritzman and Benedict²³ found that after a 6 year old fasting ram was shorn its basal metabolism was considerably higher. Under normal circumstances man instinctively compensates for a rise in metabolism by changing his environment—by going to a warm place or by using hot water bottles or by putting on additional clothing. Hamilton and Barbour²⁴ showed that when the body is exposed to cold, water leaves the blood and accumulates in and under the skin, thus acting as an emergency insulator.

The last observations may be applied as one of the explanations for the lowered basal metabolism in edematous conditions of the human frame. As water is a poor conductor of heat, any considerable edema of the integument or subcutaneous tissues should act as a suit of clothes and tend to keep the metabolism at a lower level. The fact that this pad of water acts as an insulator and protects the inward heat from reaching the surface is the probable reason that patients with edema feel cold easily and do not sweat and why in patients with such conditions, in contrast to normal persons, as a general rule the rectal heat is disproportionately higher than the body heat. The validity of this mechanism is supported by the remarkable observation that a lowered basal metabolism is the rule in other conditions, aside from nephrotic

19 Giaja, A. *Compt rend Soc de biol* **100** 1225, 1929.

20 Benedict, F. G. cited by Landauer, W. and Dunn, L. C. *J Heredity* **21**: 291, 1930.

21 Benedict, F. G., Landauer, W., and Fox, E. L. *Physiology of Normal and Frizzle Fowl with Special Reference to Metabolism*. Bulletin 177, Storrs Agricultural Experimental Station, Storrs, Conn. April 1932.

22 Boas, E. P. and Landauer, W. *Am J. M. Sc* **188** 359, 1934.

23 Ritzman, E. and Benedict, F. G. *Heat Production of Sheep Under Varying Conditions*. Bulletin 45, New Hampshire Agricultural Experimental Station, April 1931.

24 Hamilton, W. F. and Barbour, H. G. *Am J Physiol* **73** 321, 1925.

syndromes, that are associated with edema and integumentary thickening I refer especially to myxedema, to the edematous form of scleroderma, to certain forms of cardiac edema and to ichthyosis

A Myxedema The thickening of the cutaneous and subcutaneous tissues and of some of the parenchymatous tissues in myxedema is supposed to be due to a deposit of mucin, but Ord's²⁵ original observations which led to the introduction of the term myxedema into medical nomenclature have by no means been sufficiently confirmed. Some observers claimed to have found mucin in the tissues, while others reported they did not. Wegelin²⁶ in his comprehensive study of myxedema states that mucin is by no means a uniform finding and that if it is found its localization is entirely bizarre. In experimentally produced myxedema the finding of mucin in the tissues has been reported by Horsley²⁷ in apes, but Halpenny and Gunn in their experimental animals never found mucin. Krestmein²⁸ held also that the occurrence of mucin in myxedema is capricious and that it may be found in the early stages, but not in the later. In the few biopsies that have been performed in Mount Sinai Hospital in suspected cases of myxedema the presence of mucin has not been demonstrated. In view of the mass of negative evidence, one wonders, therefore, whether this disease has been correctly named. At all events, no matter what the nature of the edematous fluid may be, the fact that is of interest at present is the presence of a fluid in the tissue that acts as an insulator.

It is conventionally regarded that the lowered basal metabolism in myxedema is due to the absence or diminution of thyroid secretion and that therefore there is a direct linear relationship between the two. This cannot be accepted unconditionally in view of the observations of Blumgart and Davis,²⁹ who found after complete thyroidectomy for a cardiac disorder that although the basal metabolism usually showed appreciable lowering by the end of the first postoperative week, it did not reach its lowest values until between the end of the third and the ninth week after operation. They concluded "The first definite clinical signs and symptoms of hypothyroidism generally appeared between the first and second months after operation and usually did not occur until after the basal metabolic rate had remained low for weeks or even months." In view of the mechanism of the development of the low metabolism in the nephrotic syndrome as I have tried to outline it, it seems reasonable to wonder whether the lowering of the basal metabolism in myxedema

25 Ord, W. M. *On Myxoedema and Allied Disorders*, London, Harrison & Sons, 1898.

26 Wegelin, in Henke, F., and Lubarsch, O. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926, vol. 8, p. 344.

27 Horsley, cited by Wegelin²⁶.

28 Krestmein, G. Thesis, Hamburg, C. Holler, 1931.

29 Blumgart, H. L., and Davis, D. *Endocrinology* 18: 693, 1934.

does not bear so much a direct linear relationship to the absence of thyroid substance as an indirect one to the development of edema, especially in view of the fact that the basal metabolism does not attain its lowest level until the period when the edema becomes manifest. Obviously I do not ignore the possibility that the thyroid secretion does not suddenly escape from the body and that the organism may accumulate a sufficient reserve to act for some time or the possibility that some of the other metabolic forces may partially compensate, but the period for the development of maximum evidences of athyreosis is much longer than that witnessed after complete removal of any other endocrine organ. Hypothetic considerations aside, the only valid way to determine this point is to determine how soon thyroid substance disappears after complete thyroidectomy. Unfortunately, at present there is no accurate quantitative measure of thyroid secretion in the blood.

B The Edematous Type of Scleroderma Scleroderma is described as occurring in three stages, the edematous, the indurative and the atrophic (Ehrmann and Brunauer,³⁰ Longcope³¹). The recognition of the edematous phase of scleroderma is important not only on clinical grounds but also because, as I shall try to show, the basal metabolic rate in scleroderma varies, other factors being equal, according to the stage in which the reading is taken. It is low in the edematous phase and normal in the indurative and atrophic phases. This accounts for the wide variations in the basal metabolic readings in reported cases of scleroderma. Thus O'Leary and Nomland³² found in 38 cases that the basal metabolism was within normal limits. On the other hand, Bose and De³³ found in 5 cases that the basal metabolism was between — 16 and — 32 per cent, averaging — 23.4 per cent. From their report one cannot determine in how many of their cases the scleroderma was in the edematous phase. Ehrmann and Brunauer³⁴ in their extensive monograph on scleroderma dismiss this aspect of variation in metabolism with the assertion that the basal metabolism in scleroderma is sometimes elevated, normal or low. Longcope³¹ in a report of 8 cases recorded such figures for the basal metabolism as — 23, — 13, — 11 and — 4. One cannot ascertain from his report in which of these cases the edematous phase was present.

It has been my privilege to observe the slow evolution of the typical indurative scleroderma from the edematous phase over a prolonged period in 2 cases.

30 Ehrmann and Brunauer. Sclerodermie, in Jadassohn, J. Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol. 8, pt. 2.

31 Longcope, W. T. Hypoglycemia in Scleroderma, J. A. M. A. **90** 1 (Jan. 7) 1928.

32 O'Leary, P. A., and Nomland, R. Am. J. M. Sc. **180** 95, 1930.

33 Bose, J. P., and De, U. N. Indian M. Gaz. **69** 604, 1934.

34 Ehrmann and Brunauer,³⁰ p. 785.

REPORT OF CASES

CASE 1—L T L, a man aged 48, was first observed April 15, 1931, for a swelling of the left leg of three months' duration. The swelling appeared only during the day and disappeared after overnight rest. There was a distinct pitting edema of the left leg extending from the knee down. Physical examination revealed no manifest cause. The urine was perfectly clear. The cardiovascular system was normal, there was no evidence of phlebitis. On May 21, 1933 the condition had not altered in the least. The patient disappeared from my observation, and for the history of the subsequent course of the disease I am indebted to Drs Hauswirth and William Hitzig. The patient consulted Dr Hauswirth on Sept 14, 1938, complaining of massive swelling of the lower left extremity of eight years' duration, thickening of the skin of the hands during the past three years and changes in his voice during the past two years.

The patient was perfectly well until eight years ago, when a swelling of his left ankle developed. He consulted various physicians, who found no definite abnormality. He disregarded the persistent edema of the ankle and felt fairly well in spite of the fact that the swelling gradually ascended to involve the left leg and thigh. Four years ago he became sexually impotent. Three years ago the skin of his hands began to thicken. At this time Dr David Ball found the basal metabolic rate and electrocardiogram normal. Albumin was present in the urine. Several months later severe pains developed in his back, he was again checked up completely, but the findings were negative.

Two years ago hoarseness developed, the patient spoke in a whisper. A biopsy of the vocal cord was done, but nothing abnormal was found.

Fifteen months ago the patient underwent complete roentgen examination, but no abnormality was discovered. One year ago he was under observation at the Polyclinic Hospital. Complete studies of the blood and roentgen studies again yielded normal results. A neurologist suggested the diagnosis of muscular dystrophy. The patient was put to bed, and prostigmine was administered daily. Laryngologic examination and roentgenograms of the throat revealed no abnormality.

One year ago a hard lump on the forehead and thickenings of the face and tongue developed. He was placed under the care of Dr Cecil at the New York Hospital. A biopsy of skin taken from the shoulder region was made. No diagnosis was made, although scleroderma was definitely excluded.

Dr Foster Kennedy examined the patient and suggested quinine in large doses and testosterone propionate (oretone was the preparation used). The patient did not experience any relief. At about this time grip with high fever developed. It was observed that during this episode his voice returned to normal. Fever therapy was tried by Dr Kovacs without effect. Administration of quinine and testosterone propionate was continued for several months without any demonstrable effect. He was again given prostigmine, receiving a hypodermic injection of the methyl-sulfate and 2 tablets of the bromide daily.

Six months ago a massive edema of the right leg developed, the swelling ascended to the left gluteal region and involved the abdomen, chest wall and neck. Weakness and fatigability on walking developed, as did a marked increase in weight and slight dysphagia and vocal changes.

Physical Examination—The patient appeared chronically ill. He had a high-pitched, squeaky voice, which at times was completely lost or was replaced by a whisper. He had a fixed facial expression, and the usual facial landmarks seemed obliterated. The forehead had a few small bumps due to localized induration of the skin. The skin of the face was generally thickened and indurated and did

not pit on pressure, the lips seemed firm and unyielding, the tongue was enlarged and firm and felt like a cast made of wax. The edges of the tongue showed an immobile pattern of his teeth. The soft palate, the pillars and the pharynx were involved in this indurative process. The movements of the tongue were limited, and the patient was unable to project the tongue beyond the margin of the teeth. His neck felt firm, the induration was most marked posteriorly. The skin of the thorax was also shiny and indurated, but the respiratory excursions were not significantly limited. The lungs were clear. The heart sounds were of fair quality, no murmurs were present. The blood pressure was 96 systolic and 60 diastolic. The abdominal wall was thickened because of the induration and edema of the panniculus, the lower portion and pubic region were firm and massive and pitted slightly on pressure. No viscera could be palpated through this swollen abdominal wall. The genitalia appeared large and normal, the skin of the shaft of the penis was not wrinkled and seemed involved by the sclerosing process. The penis itself felt heavier than normal. The gluteal region was firm and immovable, and the skin felt leathery. The external inguinal rings were firm, indurated and patent and admitted one finger. There was elephantiasis of both lower extremities, of the left more than of the right. The peripheral pulses were patent. In addition to actual thickening of the skin of the lower extremities, there was also a pitting edema which extended upward to the femoral region. The skin of the hands and fingers was fairly adherent to the underlying structures and seemed immovable. It appeared shiny and atrophic. The indurative process actually interfered with flexion of the fingers so that the patient could not make a fist.

Because of the massive edema the patient's intake of fluids was limited and diuretic therapy instituted. Mercupurin was injected intravenously but was without dramatic effect. Small doses of thyroxin were given intravenously. (The patient could not tolerate thyroid by mouth because of his dysphagia.) The thyroxin was progressively increased until the patient was receiving about 10 mg. of the drug intravenously three times a week. This therapy combined with periodic injections of mercupurin gradually diminished his edema and softened and reduced slightly the sclerodermatous patches, chiefly those of the buttocks, suprapubic region, face and hands. He was also able to open his mouth more freely, and mastication was slightly improved. The anemia remained intractable and did not respond to ferrous sulfate administered by mouth in large doses or to repeated injections of liver extract given intramuscularly. On one occasion, for a period of several weeks the aforementioned therapy was discontinued and the previously noted hard swellings again became manifest. The thyroxin and mercupurin by intravenous injection and the liver extract by intramuscular injection were readministered, some clinical improvement resulted. One day the patient began to complain of pain in the chest and of shortness of breath. His lips became cyanotic and his tachypnea very marked. The respiratory frequency was out of proportion to the increased heart rate, and the clinical picture was more suggestive of pulmonary embolism than of thyroid intoxication. The patient died a few days later.

Laboratory Tests—The albumin in the urine varied between a trace and an amount sufficient to give a 1 plus reaction, dextrose was absent. Microscopic examination showed hyaline and granular casts.

The examination of the blood showed. On Oct 10, 1938, the hemoglobin content was 50 per cent, the erythrocyte count, 3,450,000, and the leukocyte count, 4,600, with polymorphonuclears 69 per cent, lymphocytes 25 per cent and monocytes 6 per cent. A smear showed anisocytosis, slight poikilocytosis and an occasional macrocyte. On October 19 the hemoglobin content was 55 per cent, the erythrocyte count, 3,300,000, and the leukocyte count, 5,200, with polymorphonuclears 63 per

cent, lymphocytes 29 per cent and monocytes 8 per cent. On October 27 the urea nitrogen content was 24 mg and the cholesterol content 165 mg per hundred cubic centimeters. On Jan 5, 1939, the cholesterol content was 210 mg per hundred cubic centimeters (both cholesterol readings were taken after thyroid therapy was instituted).

The congo red test for amyloidosis on January 9 showed a retention of 40 per cent of the dye after one hour. The urine collected one hour after the injection of the dye gave a negative reaction for congo red. In view of these findings, one must consider that there was a moderate amount of amyloidosis present.

The basal metabolic rate was -7 per cent after intensive thyroid therapy.

The electrocardiogram showed a regular sinus rhythm with a rate of 120 per minute, a left ventricular preponderance, a QRS complex slurred and of low

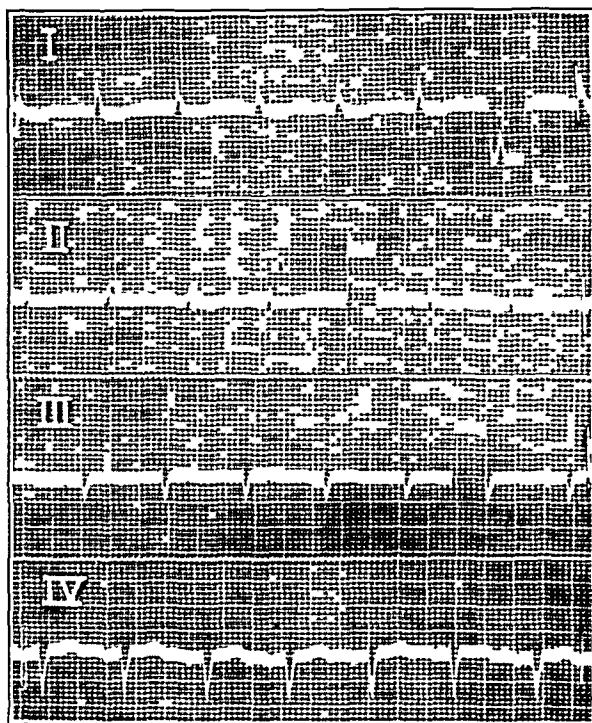


Fig 1 (case 1) —Electrocardiogram in a case of scleroderma (edematous stage) showing mainly low voltage in all leads

voltage in all leads and an RT segment slightly depressed in leads I and II and slightly elevated in leads III and IV. The T wave was semi-upright in lead I, isoelectric in lead II and equivocally isoelectric in lead III (fig 1).

Summary—In a man aged 48 who presented at first a localized edema and later a generalized edema of unknown origin and of at least five or six years' duration there eventually developed the clinical evidences of indurative scleroderma. The basal metabolism unfortunately was not determined during the earlier periods of observation, but one reading taken in the later phase, after intensive thyroid medication, showed -7 per cent, so the inference is that the basal metabolism must have been considerably lower before thyroid medication was instituted.

CASE 2—M N, a machinist 54 years of age, was admitted to the Mount Sinai Hospital Nov 16, 1938. The family history was irrelevant. Six months before the patient's admission, following trauma, pain in the lower part of the back developed. For three or four months he noted that he became cold easily

and that he felt more comfortable in hot weather. There was decrease in sweating and puffiness of the eyelids and face. The voice became thicker, and he noted stiffness and clumsiness of all his joints, especially in the fingers. There developed increased firmness of the skin, especially of the hands, paresthesia of the hands and feet, occasional tinnitus, decrease in hearing, constipation and fatigability. He noticed a distinct slowing of all activity. The mouth and tongue became sensitive to hot and spiced foods. His previously florid complexion was lost. In the past five to six months there was a decrease in sexual potency. Eight months previous to admission the patient consulted a physician for hyperhidrosis, hypertension was discovered at that time.

Physical Examination—The patient appeared well developed, well nourished, stocky and phlegmatic. The arteries of the fundus were narrow with an exaggerated reflex. The pharynx and tonsils were edematous. The thyroid gland was not palpable. The lungs were clear. The heart was enlarged to the left, the auricular second sound was louder than the pulmonic second sound, the rhythm was regular, with a rate of 90. The blood pressure was 210 systolic and 140 diastolic. The prostate gland was enlarged. The eyebrows were thin, especially laterally. The hair of the scalp, the pubis and the axilla was thin. The skin was dry and felt doughy. There was a distinct pitting edema of the lower extremities and of the face. On the acral portions of the extremities, particularly

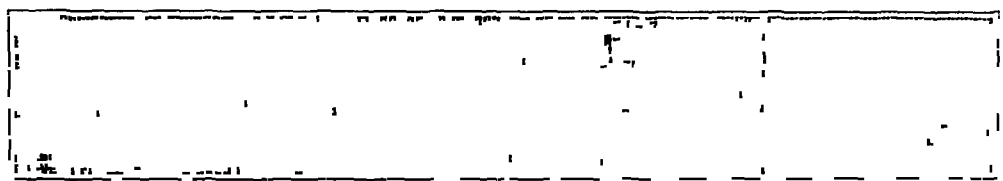


Fig 2 (case 2) —Electrocardiogram in a case of scleroderma (edematous stage) showing mainly low voltage in all leads

the palms and soles, the skin was hard and thick. On the forehead and malar eminences the skin was also thickened. The neurologic examination gave negative results. The hemoglobin content was 106 per cent. The erythrocyte count was 6,400,000, the leukocyte count was 12,300, with a normal differential count. The urea nitrogen content of the blood was 17 mg per hundred cubic centimeters, the dextrose content 85 mg, the phosphorus content 4.4 mg, the calcium content 11.2 mg and the cholesterol content 410 mg. The albumin content was 5.1 per cent and the globulin content 1.7 per cent. The icteric index was 5. The urine showed a faint trace of albumin, the specific gravity was 1.018. The venous pressure was 5.5 cm with no rise when pressure was exerted on the liver. The saccharine circulation time was thirty seconds. The sedimentation rate was three hours. A renal concentration test showed that the urine could be concentrated to a specific gravity of 1.022. A Rehfuess test revealed free acid up to 40, total acid to 65 and no blood. Roentgen examination of the chest showed a moderate diffuse dilatation of the aorta. Roentgen examination of the spine showed slight irregular hypertrophic changes and a calcified area on the right side of the abdomen, probably representing old calcified glands. The electrocardiogram revealed low voltage of the QRS complex with a normal sinus rhythm, a tendency to left ventricular preponderance, a notching and slurring of the QRS complex, a slight depression of the RT segment in leads II and III and isoelectric T waves (fig 2). The first reading of the basal metabolic rate was -14 per cent, and subsequent readings were -17 , -22 , -20 and -31 per cent. A biopsy of the skin showed no mucin.

The diagnosis was myxedema or scleroderma or a combined form of scleroderma and myxedema. The creatinine tolerance test showed an excretion within normal limits. Thyroid was given in doses up to 3 grains (0.19 Gm) daily, after 35 grains (2.27 Gm) was taken during a period of two and a half weeks, the basal metabolic rate rose from -31 to -2 per cent. The skin over the acral portions of the extremities seemed more pliable and softer. The electrocardiogram showed an increase in amplitude of the T waves. The blood cholesterol fell 275 mg per hundred cubic centimeters. The patient claimed he felt warmer. The pulse rate did not increase. He lost 11 pounds (5 Kg) in weight. The blood pressure was reduced to 145 systolic and 95 diastolic and later to 120 systolic and 80 diastolic. A dextrose tolerance test performed during the medication with thyroid revealed an elevation of blood dextrose from 100 mg to 165 mg per hundred cubic centimeters in one hour, and the patient was found to have a small amount of sugar in the urine. He was discharged and advised to return to the follow-up clinic. A recent examination of this patient (September 1939) shows that the edema is still present, although less than before, despite active medication with thyroid U. S. P. in doses of 3 grains. The evidences of scleroderma have not changed.

Summary—A man aged 54 presented a more or less generalized edema of short duration associated with typical sclerodermatous changes, especially of the face and hands. The basal metabolism was consistently low on numerous occasions. The cholesterol content was high, and the electrocardiogram showed low QRS complexes. The diagnosis rested among myxedema, scleroderma and a combination of both. It seemed that the diagnosis of a pure myxedema could be definitely excluded because a *restitutio ad integrum* of the edema on medication with thyroid was not consummated. In view of the manifest evidence of scleroderma and the fact that edema is a common predecessor or accompaniment of scleroderma, the probability is strong that the diagnosis in this case is that of an unalloyed scleroderma and not a combination of myxedema and scleroderma. Indeed, the finding of a low basal metabolism in the edematous form of scleroderma and the extraordinary tolerance of patients with such a condition for thyroid medication has led many observers to report the association of these two maladies (Ehrmann and Brunauer,³⁴ Sequeira,³⁵ Roberts,³⁶ Vallery-Radot, Pasteur, Hillemand, and Chomereau-Lamotte,³⁷ Hannay,³⁸ Rothman³⁹). The mere fact that the association of two such uncommon maladies as scleroderma and myxedema in the same persons is reported more frequently than the laws of chance would allow should make one suspect that the two are different maladies and that the edematous form of scleroderma, while simulating myxedema in many of its clinical aspects, is not identical with the disease.

C Prolonged Cardiac Failure with Edema If the thesis that a low basal metabolism is sequential to edema is correct, one would expect the same sequence of events in right-sided cardiac failure with edema of long duration. The following case report is illustrative.

35 Sequeira, J. H. *Brit J Dermat* **28** 31, 1916

36 Roberts, S. R. *M Clin North America* **12** 1429, 1929

37 Vallery-Radot, P., Hillemand, P., and Chomereau-Lamotte, B. *Bull et mem Soc med d hôp de Paris* **52** 1149, 1926

38 Hannay, M. G. *Brit J Dermat* **35** 159, 1923

39 Rothman, S. *Klin Wchnschr* **4** 169, 1925

H B, a man aged 61, was admitted to the Mount Sinai Hospital on July 28, 1939. He was in excellent health until three years before when while walking he experienced a sudden attack of shortness of breath, a sense of heaviness in the precordium and marked weakness. He was kept in bed for six weeks and soon felt well enough to do light work. Six months before he had a similar attack. He was put to bed and given digitalis, on this kind of therapy he improved. Digitalis therapy was continued, and he was given one injection of mercupurin about every four weeks. He felt fairly well as long as he stayed at home. About six weeks before admission he became dyspneic at rest and his abdomen became distended. He was again put to bed and given mercupurin three times weekly, but he showed no improvement. For the past six months he had had little appetite and had lost about 50 pounds (22.5 Kg).

Physical Examination—The lungs were moderately emphysematous, there were signs of fluid in the right part of the chest from the angle of the scapula downward. The heart was greatly enlarged to the left. The right border percussed 2 cm to the right of the sternal border in the fourth interspace. The rhythm was totally irregular. There was a loud systolic murmur all over the precordium, loudest at the apex. The blood pressure was 110 systolic and 60 diastolic. The liver extended three fingerbreadths below the costal margin, the spleen was not palpable. Both lower extremities were markedly edematous.

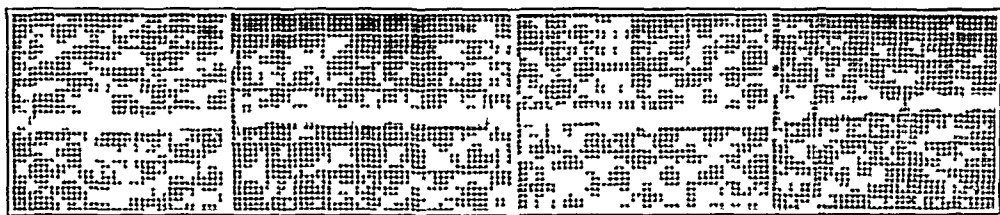


Fig 3—Electrocardiogram in a case of right-sided cardiac failure with anasarca but without dyspnea showing low voltage and auricular fibrillation

Diagnosis—The diagnosis was arteriosclerotic heart disease, coronary occlusion (?), auricular fibrillation, congestive heart failure, right hydrothorax, rheumatic heart disease (?).

Laboratory Data—On admission, the blood count showed hemoglobin content 109 per cent and leukocytes 15,700, with a differential count of segmented polymorphonuclears 78 per cent, nonsegmented polymorphonuclears 14 per cent, lymphocytes 6 per cent, mononuclears 1 per cent and basophils 1 per cent. The venous pressure was 4 cm. The urea content of the blood was 18 mg per hundred cubic centimeters, the dextrose content 115 mg, the cholesterol content 385 mg and the total protein content 5.4 mg. The icteric index was 21. The Wassermann reaction of the blood was negative. The basal metabolism was -16 per cent. On September 12, the basal metabolism was -20 per cent. The blood protein on four occasions varied between 4.6 and 6.0 mg per hundred cubic centimeters. The blood cholesterol on September 5 was 270 mg and on September 20, 385 mg per hundred cubic centimeters. The total blood volume was 97 cc per kilogram, a high normal value. The urine concentrated to 1018 and showed albumin at all times, varying between a trace and an amount sufficient to give a 2 plus reaction.

The electrocardiogram on July 29 showed auricular fibrillation and a QRS complex of moderately low voltage and slightly slurred. The T waves were low in the standard leads (fig 3). Subsequent electrocardiograms showed no change except on one occasion, when ventricular extrasystoles were present.

Roentgen examination of the chest at the time of the patient's admission showed a generalized enlargement of the heart. The lungs were markedly congested, and there were a few irregular deposits in the right lung which might have represented infarcts. A subsequent roentgenogram (made September 9) showed a disappearance of the previous infiltrations.

Summary—A man aged 61 had a history of a coronary closure occurring three years previously and another of six months' duration. Six weeks previous to admission, ascites developed. The patient revealed evidence of right-sided cardiac failure with generalized anasarca. The basal metabolism readings were -16 and -20 per cent. The blood cholesterol was 270 and 385 mg per hundred cubic centimeters. The electrocardiographic curve, in addition to auricular fibrillation, showed low voltage and slight slurring of the QRS complexes.

In acute cardiac failure with dyspnea, tachycardia and edema of recent origin any tendency toward a lowering of the basal metabolism would be neutralized by an elevation consequent on the usually attendant dyspnea and tachycardia. Moreover, the probability is strong that an edema of only short duration would not have much effect on the basal metabolic rate.

D Ichthyosis In the conditions I have described, namely, the nephrotic syndrome, myxedema, the edematous form of scleroderma and prolonged right-sided failure with edema, the "suit of clothes" is not limited to the integument but invades to a greater or lesser extent the interstitial and even parenchymatous tissues. Many are familiar with the occurrence of fluid in the serous surfaces in nephrotic syndromes and in right-sided cardiac failure and with the occurrence of fluid in the cardiac muscle in myxedema, causing "myxedema heart." In scleroderma, not only are changes in the mucous membranes of the upper part of the digestive and of the respiratory tract common, but even interstitial changes in the muscles and parenchymatous organs are found (Ehrmann and Biunauer³⁰). In ichthyosis, on the other hand, the "suit of clothes" is exclusively limited to the skin, and the thickening, according to Porter,⁴⁰ is the result of an increased cornification, an exaggerated production of epidermal scales and a greatly thickened stratum corneum. Nevertheless, it is an interesting confirmation of my thesis that despite this limitation the basal metabolism in many cases in ichthyosis is lowered. Thus, Bose and De³³ found in 18 patients with ichthyosis that the basal metabolism varied between -12 per cent and -37 per cent, averaging -27.5 per cent. Porter⁴⁰ found the basal metabolism below normal in 70 per cent of 10 children with ichthyosis, while in adults it was below normal in 25 per cent. In 1 case, that of a girl aged 13 observed by Dr. Samuel Averbuck, the basal metabolic rate was -25 per cent, and the pulse rate was 76. This girl was physically normal in every other respect.

40 Porter, A. Brit J Dermat 38 475, 1926

The low basal metabolic rate in ichthyosis together with the notorious tolerance of patients with this condition for thyroid medication led many dermatologists to regard ichthyosis as a disease of metabolism. The association also explains, as in scleroderma, the not infrequent reports of the occurrence of myxedema and ichthyosis in the same patient (Porter ⁴⁰)

SIGNIFICANCE OF THE BLOOD CHOLESTEROL LEVEL IN EDEMATOUS STATES

In addition to the causal relationship between edematous states and the lowered basal metabolic states, it is a remarkable fact that in most of the conditions I have described the blood cholesterol values were elevated. The question arises whether it is the edema or the metabolic rate that influences the blood cholesterol level. Epstein and Lande ⁸ in 1922 called attention to the relationship between the basal metabolic rate and the blood cholesterol in thyroid disease, the rate being low with a high cholesterol level and vice versa. In true myxedema the blood cholesterol is uniformly high, while hyperthyroid conditions tend to diminish the level of the cholesterol in the blood (Mason, Hunt and Hurxthal ⁴¹). However, as these observers point out, there is no definite correlation between the basal metabolism and the blood cholesterol. Moreover, low metabolic rates may be accompanied by a normal or a diminished value for blood cholesterol. For instance, in Addison's disease and in anorexia nervosa, maladies in which the basal metabolism is low, the cholesterol values are likewise low. Confirmation of the lack of correlation between the basal metabolism and the blood cholesterol is furnished by the observations of Grant and Schube ⁴² and Cutting, Rytand and Tainter ⁴³ based on the results of medication with alphadinitrophenol. Grant and Schube demonstrated that the blood cholesterol after administration of alphadinitrophenol usually showed a deviation from the normal, which was usually in a positive direction. The range of this deviation was not the same in all cases. In some, the blood cholesterol after a preliminary rise dropped below normal before stabilizing itself within the original range. Cutting, Rytand and Tainter showed that the correlation between the basal metabolic rate and the blood cholesterol level was not present when the metabolism was raised by administration of sodium alphadinitrophenol and concluded that the blood cholesterol content is not related directly to the metabolic rate but is influenced by other actions of the thyroid

41 Mason, R. L., Hunt, H. M., and Hurxthal, L. M. *New England J Med* **203** 1273, 1930

42 Grant, L. F., and Schube, P. G. *J Lab & Clin Med* **29** 56, 1934

43 Cutting, W. C., Rytand, D. A., and Tainter, M. L. *J Clin Investigation* **13** 547, 1934

secretion It is a fair presumption, therefore, that the elevated blood cholesterol in my cases was not directly consequent on the low metabolic rate, but depended on some other factor or factors Whether the edema alone is directly or indirectly responsible for the elevated cholesterol cannot, in the light of the complexities of cholesterol metabolism, be answered with any assurance, but the possibility certainly is suggestive Certainly, one may assert that the factor that brings about edema is not responsible, because in the conditions that I have described the mechanisms are entirely diverse It would appear that the elevated blood cholesterol in edematous states is either a compensatory or a teleologic phenomenon, but the nature of this phenomenon is, in the present state of knowledge, entirely speculative

SIGNIFICANCE OF THE LOW VOLTAGE IN ELECTROCARDIOGRAPHIC TRACINGS IN EDEMATOUS STATES

A low voltage in the electrocardiogram, both of the QRS complex and of the T waves, is conventionally regarded as characteristic of myxedema and is supposed to be due to myxedematous infiltration of the heart muscle It is apparent that such an electrocardiogram is by no means characteristic of the so-called myxedema heart, because identical electrocardiographic tracings are found in all the edematous conditions I have described, namely, "nephrotic syndromes," the edematous form of scleroderma and certain forms of right-sided cardiac failure The mechanism whereby such low electrocardiographic tracings are produced in edematous states is not clear Poor conductivity arising from the edematous skin cannot be the cause, because identical curves are obtained by use of needle electrodes that pierce the skin It is conceivable that edema of the myocardium may be the mechanism causing the low voltage, a mechanism that has been advanced to explain the characteristic low voltage in the electrocardiogram of the "myxedema" heart Such an explanation may be valid in conditions of anasarca but cannot account for the low voltage witnessed in maladies such as the edematous form of scleroderma or ichthyosis, in which the "suit of clothes" is strictly integumentary⁴⁴ That the low voltage bears a direct relationship to the low metabolic rate is shown by observations on patients with anorexia nervosa, in whom the basal metabolism is notoriously low and in whom no form of edema or integumentary thickening is present

Of 8 cases of anorexia nervosa observed in the Mount Sinai Hospital during the past few years, electrocardiograms were taken in 2 cases In both there was low voltage

44 The same reasoning applies to the possibility that a pericardial effusion may cause the low voltage As a matter of fact, a pericardial effusion was not demonstrable in any of the cases that I have cited

A girl 17 years of age gave a history of the loss of 20 pounds (9 Kg) of weight, anorexia and amenorrhea. The basal metabolic rates on three occasions were —23, —25 and —26 per cent. The value for blood cholesterol was 310 mg per hundred cubic centimeters. The electrocardiogram showed a low voltage of both the QRS complexes and the T waves.

A boy aged 14 gave a history of anorexia and a decrease in weight from 137 pounds to 88 pounds (40 Kg). The value for blood cholesterol was 240 mg per hundred cubic centimeters. The basal metabolic rates were —47, —49 and —51 per cent. The electrocardiogram showed low QRS complexes in leads I, III and IV. In lead II they were normal. The T waves were low in leads I and IV.

SUMMARY AND CONCLUSIONS

None of the previously considered hypotheses for the explanation of the lowered basal metabolism in "nephrosis" is adequate. Evidence is adduced to prove that the condition is due to the edematous fluid which acts as a suit of clothes, thereby preventing conduction, radiation and convection of heat. This mechanism of the lowered metabolism applies not only to "nephrosis" but to other conditions accompanied by edema or integumentary thickenings. I refer especially to myxedema, the edematous form of scleroderma, chronic edematous right-sided cardiac failure unassociated with dyspnea, and ichthyosis. Concomitant findings in these conditions associated with a lowered basal metabolism are (1) a low electrocardiographic curve indistinguishable from that of the myxedema heart and (2) a high level of cholesterol in the blood. Finally, these conditions are characterized by an unusual tolerance for the administration of thyroid preparations.

PERSONS LACKING SWEAT GLANDS

HEREDITARY ECTODERMAL DYSPLASIA OF THE ANHIDROTIC TYPE

F WILLIAM SUNDERMAN, M D, P H D

PHILADELPHIA

Studies are reported on 3 patients with hereditary ectodermal dysplasia. With the exception of the family described by Darwin,¹ this is apparently the first report of the affliction occurring in three members of one family in the same generation. Special studies on these persons include serum analyses and observations on the effect of exposure to high environmental temperatures.

The literature pertaining to hereditary ectodermal dysplasia has been reviewed by MacKee and Andrews,² Weech,³ Gordon and Jamieson,⁴ Lord and Wolfe,⁵ de Silva⁶ and others. In 1929 Weech listed 10 cases of this unusual condition, in 1931 Gordon and Jamieson listed 21 cases, and more recently, in 1938, Lord and Wolfe tabulated in chronologic order more than 40 cases described in the literature together with a bibliography pertaining to them.

The salient features of the disease are the absence of sweat glands and occasionally of lacrimal glands, the growth of scanty, fine lanugo type of hair, the total absence or incomplete development of teeth, and the presence of chronic rhinitis, frequently associated with loss of the sense of smell. Weech, in 1929, proposed for the name of this syndrome hereditary ectodermal dysplasia of the anhidrotic type, since (1) the

From the Medical Division of the Hospital of the University of Pennsylvania, the Department of Research Medicine and the William Pepper Laboratory of Clinical Medicine.

1 Darwin, C. The Variation of Animals and Plants Under Domestication, New York, D Appleton and Company, 1896, vol 2, p 319.

2 MacKee, G M, and Andrews, G C. Congenital Ectodermal Defect, Arch Dermat & Syph **10** 673 (Dec) 1924.

3 Weech, A A. Hereditary Ectodermal Dysplasia (Congenital Ectodermal Defect), Am J Dis Child **37** 766 (April) 1929.

4 Gordon, W H, and Jamieson, R C. Hereditary Ectodermal Dysplasia of the Anhidrotic Type, Ann Int Med **5** 358, 1931.

5 Lord, L W, and Wolfe, W D. Hereditary Ectodermal Dysplasia of the Anhidrotic Type (Congenital Ectodermal Defect), Arch Dermat & Syph **38** 893 (Dec) 1938.

6 de Silva, P C C. Hereditary Ectodermal Dysplasia of the Anhidrotic Type, Quart J Med **8** 97, 1939.

tissues principally affected were of ectodermal origin, (2) the condition represented a developmental anomaly and (3) the data gave evidence of a hereditary tendency

Various authors⁷ attributed the report of the first case to Wedderburn, in 1838. According to Lord and Wolfe, however, the first report was published by Thurnam⁸ in 1848, when he described 2 cases. I have been unable to find any reference to Wedderburn's report except the following excerpt from Darwin's writings, cited by Cockayne⁹

I may give an analogous case, communicated to me by Mr W Wedderburn, of a Hindoo family in Scinde, in which ten men, in the course of four generations, were furnished in both jaws taken together, with only four small and weak incisor teeth and with eight posterior molars. The men thus affected have little hair on the body, and become bald early in life. They also suffer much during hot weather from excessive dryness of the skin.

The literature relating to the symptomatology of this developmental anomaly has been reviewed in detail by several authors, notably Smith,¹⁰ MacKee and Andrews,² Weech³ and Clouston¹¹

HISTORY AND PHYSICAL EXAMINATIONS

For the sake of brevity the histories of these persons will not be recorded separately but will be discussed as a group.

Three brothers, P. B., who is 22 years of age, J. B., who is 20, and A. B., who is 5, are members of a family of 10 children of Italian parents. On cursory survey the parents and the other 7 children appear normal and relatively healthy and present no apparent congenital defects. Although no accurate genealogic data have been obtainable, it is asserted that the grandparents, aunts, uncles and cousins presented none of the defects observed in these 3 brothers.

The chief complaints of these patients are fever and headache when exposed to high temperatures. The patients are said to have appeared normal at birth and during early infancy. However as they grew older, normal deciduous teeth failed to develop, they never perspired and 2 of them were unable to shed tears. In childhood their noses became of

7 (a) Thannhauser, S. J. Hereditary Ectodermal Dysplasia of the "Anhydrotic Type" with Symptoms of Adrenal Medulla Insufficiency and with Abnormalities of Bones of Skull, *J. A. M. A.* **106** 908 (March 14) 1936. (b) Jadassohn, J. *Handbuch der Haut- und Geschlechtskrankheiten*, Berlin, Julius Springer, 1932, vol. 4, pt. 1, p. 43. (c) de Silva⁶

8 Thurnam, J. Two Cases in Which the Skin, Hair, and Teeth Were Very Imperfectly Developed, *Med-Chir. Tr.*, London **31** 71, 1848.

9 Cockayne, E. A. Inherited Abnormalities of the Skin and Its Appendages, New York, Oxford University Press, 1933, p. 218. Darwin¹

10 Smith, J. Hereditary Ectodermal Dysplasia, *Arch. Dis. Childhood* **4** 215 1929.

11 Clouston, H. R. The Major Forms of Hereditary Ectodermal Dysplasia (with Autopsy and Biopsies on Anhydrotic Type), *Canad. M. A. J.* **40** 1, 1939.

the saddle type and their lips negroid in appearance. Hair failed to appear over their extremities, and the hair of the scalp, pubis and axillas was sparse. The 2 older boys complained of a continuous, fetid nasal discharge since childhood and observed that they had lost their ability to distinguish odors.

During their school days it was discovered that the 2 older boys frequently had fever during warm weather. A positive Mantoux reaction was obtained on the oldest patient, and he was advised to enter a sanatorium for tuberculosis, which he refused to do. As a compromise, however, this patient entered the University Hospital for study in August 1936, at which time the ectodermal defect was recognized. Since that admission the patient and his 2 brothers have been under my observation at infrequent intervals.

The patients have been extremely intolerant of high temperatures. During the past few summers the 2 older patients have found it necessary to apply water over their underclothing in order to keep reasonably cool. During the daytime in the summer months they spend much of their time in swimming pools. On warm nights they sleep on the cellar floor in order to keep comfortable. Neither of the 2 older patients is capable of performing physical work during the summer months. The oldest one tried working as a caddy for two or three days, however, when exposed to the sun he would collapse and the application of cold water was required to revive him.

At intervals during the periods of observation the 2 older patients kept records of their oral temperature. During March and April their temperatures, taken four times daily, ranged from 97.4 to 98.6 F, during July and August their temperatures ranged from 97 to 102.6 F. The lowest temperatures were usually observed during the morning hours and the highest in the afternoon and evening hours. The daily oscillations during the summer months usually amounted to 3 degrees (F) or more. Increase in the respiratory and pulse rates was coincident with elevations in the temperature.

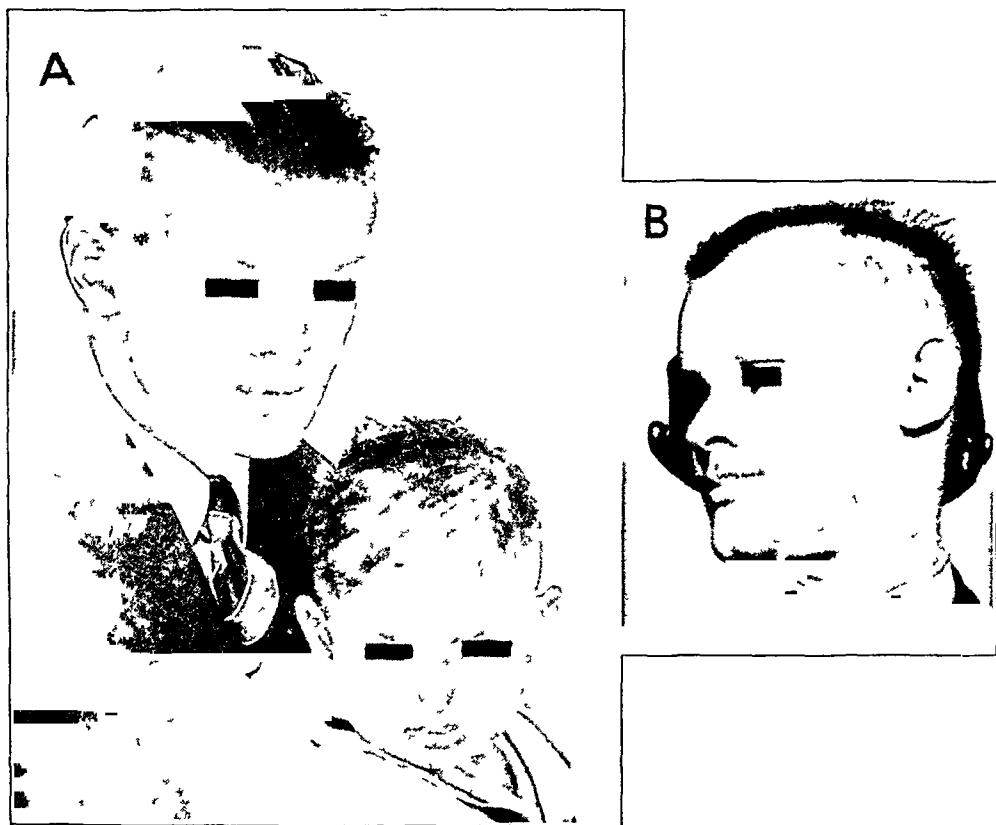
The 3 brothers have all been alert, cooperative and of normal intelligence. Indeed, the 2 older patients graduated from high school and held rank in the upper third of their classes. This fact probably would not be suspected from their facies (figure). It is noteworthy that the published photographs of patients with this dysplasia exhibit a similarity of features.¹² It has been pointed out especially by Touraine.¹³

12 (a) Janitzkaja, E., and Rjabow, M. Ein ausgebreiteter Ektodermaldefekt, *Ztschr f klin Med* **107** 381, 1928. (b) Loewy, A., and Wechselmann, W. Zur Physiologie und Pathologie des Wasserwechsels und der Warmregulation seitens des Hautorganes, *Virchows Arch f path Anat* **206** 79, 1911. (c) MacKee and Andrews.² (d) Gordon and Jamieson.⁴ (e) Lord and Wolfe.⁵ (f) Thannhauser.^{7a}

13 Touraine, A. L'anhydrose avec hypotrichose et anodontie, *Presse med* **44** 145, 1936.

that in certain cases the resemblances are so striking that patients with this affliction might easily be supposed to be members of the same family

A description and photographs of the teeth and jaw of the oldest patient, P B, have been published recently by Dr T J Cook,¹⁴ the dental consultant of the hospital. P B has 4 rudimentary, peg-shaped canine and molar teeth, J B has 6, and A B has 5. The alveolar ridges in the lower jaw are poorly developed in each patient. The skin is dry, smooth and velvety. Several pigmented areas, present over both arms and chest of J B, are alleged to have been the result of burns received in childhood.



A, photographs of P B and A B, demonstrating saddle noses and thick, protrusive lips, *B*, photograph of J B, demonstrating the lanugo-like character of the hair

Roentgenograms of the lungs of the oldest patient revealed no evidence of parenchymal disease. P B and J B had roentgenographic signs of thickening of the mucous membranes of the frontal and ethmoid sinuses.

The results of urinalyses and the blood counts of the 2 older patients were normal. The Wassermann reactions of the blood of these patients

¹⁴ Cook, T G. Hereditary Ectodermal Dysplasia of the Anhidrotic Type, *Am J Orthodontics* 25 1008, 1939

were repeatedly negative. The basal metabolic rate of J B was +20 per cent. The sugar tolerance curve of J B, determined after the ingestion of 100 Gm of dextrose, proved to be of mild diabetic type. At the one hour period the blood sugar was 180 mg and at the two hour period 130 mg per hundred cubic centimeters. The sugar tolerance curve of P B was of normal type.

No laboratory data have been obtainable in the case of the youngest brother.

RESULTS OF SPECIAL STUDIES

Studies of the nail beds by Dr J Q Griffith indicated the presence of a larger number of capillaries than he ordinarily observes in normal

TABLE 1—*Analyses of Serums*

	P B	J B
	mEq per L	mEq per L
Total base (chemically determined)	143.6	144.2
Sodium	133.5	133.3
Potassium	3.6	3.9
Calcium	5.4	5.3
Magnesium	1.6	1.6
BCl	100.5	101.4
BHCO ₃ *	26.4	25.0
(B ₂ HPO ₄ + BH ₂ PO ₄)†	2.1	
BPr ‡	12.6	11.3
	Mg per 100 Cc	Mg per 100 Cc
Cholesterol	133	147
Sugar	100	65

* BHCO₃ = (CO₂) - 1.27

† B₂HPO₄ = $\frac{77}{23}$ (PO₄)
BH₂PO₄, assuming p_H 7.4 = $\frac{77}{23}$ (PO₄)

B₂HPO₄ + BH₂PO₄ = mEq PO₄

‡ BPr = 0.97 (Pr) (p_H - 5.26)

Pr = grams of protein per hundred cubic centimeters

persons. Measurement of the cardiac output in J B showed it to be within the normal range.

Specimens of skin from the axillae of the 2 older patients were obtained for biopsy. The sections were examined by Dr F D Weidman, who reported a total absence of eccrine (sweat) glands in both patients. The apocrine forms, however, were highly developed, although the involuntary muscle around them was hypoplastic.

Serum Analyses—Chemical analyses of the blood serum were made on specimens obtained from the 2 older patients (table 1). Except for diminished concentrations of magnesium in the serum of both patients, the composition with respect to electrolytes was within the normal range. The slight decrease in the concentration of magnesium

in these patients is of interest and might have been anticipated, since increase is observed in persons with prolonged hypothermia¹⁵ and in hibernating animals¹⁶

The concentration of cholesterol was diminished in the serum of both patients

Effect of Increasing the Environmental Temperature—Various writers have reported that persons devoid of sweat glands may show increases of 2 degrees (F) or more in the body temperature after exercise, after the ingestion of hot drinks or even on being wrapped too warmly (Tendlau,¹⁷ Janitzkaja and Rjabow,^{12a} Smith,¹⁰ MacKee and Andrews²) Tendlau and Wechselmann and Loewy observed that exposure of patients to heat accelerated the respiratory rates, which they regarded as a means of increasing heat dissipation comparable to panting in dogs Wechselmann and Loewy demonstrated in their patients that the skin lost as much water by insensible perspiration as did that of normal persons Hiebert and Garland¹⁸ observed that the cutaneous temperatures in their patient, a child lacking sweat glands, equaled those of children with sweat glands who had rectal temperatures of 104.5 F

Richardson¹⁹ made calorimetric studies on the patient whose case was reported by MacKee and Andrews He demonstrated that 28 per cent of the total heat eliminated by this patient during the resting state was in the form of water vapor, as compared with 25 per cent found for normal persons by Soderstrom and Du Bois²⁰ Richardson's studies indicated that in the resting state the patient without sweat glands was capable of vaporizing water normally through the skin and lungs However, after exercise the elimination of water through the skin and lungs was not increased and the body temperature rose

15 Sunderman, F. W., Burton, A. C., and Horak, H. M. Unpublished data. Lustig, B., Ernst, T., and Reuss, E. Die Zusammensetzung des Blutes von Helix pomatia bei Sommer- und Wintertieren, *Biochem Ztschr* **290** 95, 1937

16 Suomalainen, P. Magnesium and Calcium Content of Hedgehog Serum During Hibernation, *Nature*, London **141** 470, 1938, Production of Artificial Hibernation, *ibid* **142** 1157, 1938

17 Tendlau, B. Ueber angeborene und erworbene Atrophia cutis idiopathica, *Virchows Arch f path Anat* **167** 465, 1902

18 Hiebert, J. M., and Garland, J. Hereditary Ectodermal Dysplasia of the Anhidrotic Type, with Case Report, *New England J Med* **210** 784, 1934

19 Richardson, H. B. Clinical Calorimetry XL The Effect of the Absence of Sweat Glands on the Elimination of Water from the Skin and Lungs, *J Biol Chem* **67** 397, 1926

20 Soderstrom, G. F., and Du Bois, E. F. Clinical Calorimetry XXV The Water Elimination Through Skin and Respiratory Passages in Health and Disease, *Arch Int Med* **19** 931 (May) 1917

In table 2 are given data obtained during an experiment in which the 2 older patients (P B and J B) and 2 control subjects (McG and F W S) were placed in a hot room for a period of thirty minutes. These 4 persons, under basal conditions, undressed and entered a room having a dry bulb temperature of 74 F and an effective temperature of 68 F. After the subjects had rested in this room for approximately fifteen minutes, readings of the cutaneous and oral temperatures were taken and the subjects were weighed. They then entered a heated room having a dry bulb temperature of 100 F and an effective temperature of 86 F. They remained in this room for thirty minutes, after which measurements of the cutaneous and oral temperatures were again made and the body weights obtained.

TABLE 2—Measurements After Change in Environmental Temperature

	Room Temperature, F		Average Skin Temperature, F	Oral Temperature, F	Loss of Weight, Skin and Lungs, Gm	Urine, Gm
	Dry Bulb	Effective				
Fifteen Minutes' Exposure to Moderate Temperature						
Patients						
J B	74	68	93.0	98.4		
P B	74	68	94.6	97.8		
Control subjects						
McG	74	68	90.9	98.4		
F W S	74	68	90.9	98.4		
Thirty Minutes' Exposure in Hot Room						
Patients						
J B	110	86	104.0	101.4	22	270
P B	110	86	102.8	102.0	15	150
Control subjects						
McG	110	86	99.6	98.6	262	10
F W S	110	86	97.8	98.4	360	20

The cutaneous temperatures were measured at fifteen areas of the body surface by means of a thermocouple. The values given in the table represent the average of these measurements.

The effective temperature represents a composite value obtained by the measurements of dry bulb and wet bulb temperatures and air movements.²¹ Sweating usually occurs at effective temperatures of 78 to 80 F.

After twenty minutes' exposure in the hot room the patients without sweat glands became hyperpneic, panting somewhat like dogs. Both felt sick. Their skins remained dry and velvety, and no moisture could be detected anywhere on the surface of their bodies. After thirty minutes' exposure the average cutaneous temperatures of J B and P B increased to 104 and 102.8 F and the oral temperatures to 101.4 and 102 F, respectively. The temperatures of the control subjects remained

21 Bazett, H. C. Physiological Responses to Heat, *Physiol. Rev.* 7: 531, 1927.

within the normal range. The control subjects lost 262 and 360 Gm, respectively, by way of the skin and lungs, the patients lost only 22 and 15 Gm by the same channels. The loss of weight in the 2 patients during the period of exposure in the hot room corresponded approximately to the amount of insensible loss occurring in normal persons under resting conditions,²² i. e., 20 to 40 Gm per hour. Diuresis developed in both patients, but not in the control subjects. A half-hour after leaving the hot room the patients still felt "shaky," at which time their oral temperatures had fallen to 99.4 (J. B.) and 100.2 F (P. B.)

COMMENT

The body temperatures of subjects J. B. and P. B. were increased approximately 1.2 degrees C (3.6 degrees F) in the hot room. Their respective weights were 50.1 and 51.0 Kg. If the average value of 0.83²³ is assumed to be the specific heat of their bodies, then the total heat gained may be roughly estimated as from 80 to 85 calories during a thirty minute period of exposure (i. e., a rate approximately 4,000 calories per day). This balance would presumably comprise the heat derived from body metabolism and the radiant energy received from the hot room, minus the loss of heat by evaporation through the skin and lungs. When one allows for an increased basal metabolic rate of 20 per cent, as observed in patient P. B., as well as a further increase as a result of the hyperthermia, it is readily demonstrated that under the conditions of this experiment the probable caloric loss was considerably less than the probable caloric production.

The reason for the diuretic response in the patients remains speculative. The suggestion is offered that the diuresis might be related to the severe hyperpnea that occurred during exposure to the high environmental temperature. Hyperpnea of the degree witnessed in these patients might be expected to produce alkalosis. Bazett²⁴ and others have shown that alkalosis induced by hyperpnea is usually associated with diuresis. An obvious alternative hypothesis might also be offered, namely, that elevated temperatures may lead to the liberation of water from tissues to supply the sweat glands but in the absence of sweat glands this water escapes by way of the kidneys.

An item in the record of the 2 older patients may deserve emphasis. During their school years medical attention was focused principally on

22 Benedict, F. G., and Root, H. F. Insensible Perspiration. Its Relation to Human Physiology and Pathology, *Arch. Int. Med.* **38**: 1 (July) 1926.

23 Burton, A. C. Human Calorimetry. II. The Average Temperature of the Tissues of the Body, *J. Nutrition* **9**: 261, 1935.

24 Bazett, H. C. Studies on Effects of Baths on Man. I. Relationship Between the Effects Produced and the Temperature of the Bath, *Am. J. Physiol.* **70**: 424, 1924.

their unexplained fever. It had apparently not occurred to any one to try to correlate the fever with increase in environmental temperature and the inability to sweat. A survey of the literature suggests²⁵ that ectodermal defects may not always be as extensive as those observed in these patients. Diminution in the number of teeth is not infrequently observed. Although, so far as I am aware, partial development of or diminution in the number of sweat glands has not been described, nevertheless it is well known that persons may vary considerably in their ability to sweat, and it is recognized that sweating may even be unilateral. Moreover, such factors as drugs, faradic stimulation and emotional reactions may all influence the sweating response. Since the eccrine glandular system normally provides a channel for loss of heat during periods of excessive heat production, it is suggested that in certain persons suffering with unexplained fever, the sweating response might profitably be investigated.

SUMMARY

Studies are reported in 3 cases of hereditary ectodermal dysplasia of the anhidrotic type occurring in the same family.

The effects produced by exposure to a high environmental temperature for thirty minutes were studied in 2 of the patients and were compared with those produced in 2 control subjects. In the patients devoid of sweat glands the loss of weight through the skin and lungs corresponded approximately to the amount of insensible loss normally occurring in resting persons at normal temperatures, in the 2 control subjects the loss of weight amounted to about sixteen times as much during the same period of exposure. In the 2 patients hyperpnea and diuresis ensued, in the control subjects they did not.

These studies emphasize the importance of the sweat glands in providing a mechanism for the dissipation of heat when the demands of the body require greater elimination of heat than is needed in the normal resting state.

Serum analyses on 2 of the 3 patients indicated slightly decreased concentrations of magnesium and of cholesterol.

²⁵ Weber, F. P. A Note on Combined Congenital Ectodermal Defects, *Brit J Child Dis* 26:270, 1929. de Silva.⁶

CLINICAL USE OF SULFAMETHYLTHIAZOLE

W H KAMMERER, M D

MENNASCH KALKSTEIN, M D

AND

SAUL SOLOMON, M D

NEW YORK

Since the introduction of chemotherapeutic agents effective in the treatment of streptococcal and pneumococcal infections, efforts have been made to improve on these agents and to develop a compound equally effective against infections caused by staphylococci. Sulfathiazole (2-sulfanilamidothiazole) and sulfamethylthiazole (2-sulfanilamido-4-methylthiazole) have shown promise in this direction.

Sulfamethylthiazole is a white amorphous powder which is less soluble than sulfanilamide, sulfapyridine or sulfathiazole. Sulfamethylthiazole (together with sulfathiazole) was first synthesized in August 1939 by Fosbinder and Walter,¹ who also reported its effectiveness against streptococci and pneumococci. Lawrence² found sulfathiazole and sulfamethylthiazole to be superior to sulfanilamide in their bacteriostatic effect against Lancefield group A *Streptococcus haemolyticus* and against the colon-typhoid-dysentery group. Barlow and Homburger³ reported that in experimentally produced infections with *Str. haemolyticus* and *Pneumococcus* types I, II and III the effect of thiazole derivatives of sulfanilamide was definitely superior to that of the parent substance and compared favorably with that of sulfapyridine. However,

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Sulfamethylthiazole has not been licensed for sale in the United States

From the Second (Cornell) Medical Division and the Fourth Medical Division, Bellevue Hospital, the New York Hospital, and the Department of Medicine, Cornell University Medical College

1 Fosbinder, R. F., and Walter, L. A. Sulfanilamido Derivatives of Heterocyclic Amines, *J. Am. Chem. Soc.* **61** 2032, 1939

2 Lawrence, C. A. Bacteriologic Actions of Three Thiazol Derivatives of Sulfanilamide upon Bacteria in Broth Cultures, *Proc. Soc. Exper. Biol. & Med.* **43** 92, 1940, Bacteriostatic Effects of Sulfanilamide, Sulfapyridine and the Thiazol Derivatives, in Colon-Typhoid-Dysentery Group, *ibid.* **44** 162, 1940

3 Barlow, O. W., and Homburger, E. Thiazol Derivatives of Sulfanilamide and Effect on Beta-Hemolytic *Streptococcus* and *Pneumococcus* Infections in Mice, *Proc. Soc. Exper. Biol. & Med.* **43** 317, 1940, Specific Chemotherapy of Experimental *Staphylococcus* Infections with Thiazol Derivatives of Sulfanilamide, *ibid.* **42** 792, 1939

unlike sulfanilamide and sulfapyridine, the thiazole derivatives were found to exert a marked effect against staphylococci both in vitro and in vivo

Weilbaecher and his co-workers⁴ reported 4 cases of typhoid fever in which the patients were successfully treated with sulfamethylthiazole Carroll and his associates⁵ reported 5 cases of staphylococcic infection, in 2 of which cultures of the blood were positive for the organisms In all cases the patients responded well to treatment with sulfamethylthiazole, with no toxic effects Grulee and Mason⁶ reported the use of sulfamethylthiazole in the cases of 3 children with staphylococcic furunculosis of the scalp There was improvement in all, but 2 of the children showed evidence of toxic effects, namely, vomiting, toxic rash and neutropenia, which disappeared when the drug was withdrawn

Herrell and Brown⁷ reported the successful use of sulfamethylthiazole in a case of severe septicemia caused by *Staphylococcus aureus* and in 1 of lobal pneumonia due to a mixed infection

CLINICAL MATERIAL

Since January 1940 we have had an opportunity to use sulfamethylthiazole⁸ clinically in 53 cases, in 22 of which the patients were suffering from pneumonia The remaining 31 cases were a heterogeneous group, but the largest number (19) were cases of staphylococcic infection For convenience in analyzing the therapeutic effect of sulfamethylthiazole we have divided our clinical material into three main groups, namely, the pneumonias, the staphylococcic septicemias and staphylococcic and other infections In the entire series of cases we have made observations to determine the absorption, the therapeutic effect and the toxicity of the drug

ABSORPTION STUDIES

Figure 1 shows the composite curves representing the concentration of sulfamethylthiazole in the blood of 4 patients who each received a single oral dose of sulfamethylthiazole Two of the patients received

4 Weilbaecher, J O, Jr, Moss, E S, Taylor, H M, and Dupuy, H Treatment of Typhoid Fever with Thiazole Derivatives of Sulfanilamide Preliminary Report of Four Cases, *South M J* **33** 645, 1940

5 Carroll, G, and others Sulfamethylthiazole Report of Its Clinical Use in *Staphylococcus* Septicemia with Apparent Success, *South M J* **33** 83, 1940

6 Grulee, C G, and Mason, J T New Treatment of Furunculosis (Sulfamethylthiazol), *J Pediat* **15** 549 (May) 1940

7 Herrell, W E, and Brown, A E The Clinical Use of Sulfamethylthiazole in Infections Caused by *Staphylococcus Aureus* Preliminary Report, *Proc Staff Meet, Mayo Clin* **14** 753, 1939

8 The drug was supplied by the Lederle Laboratories, Inc, and the Winthrop Chemical Co, Inc

2 Gm, the other 2 received 3 Gm. The maximum rise occurred in four hours, and at the end of twenty-four hours only traces could be detected in the blood.

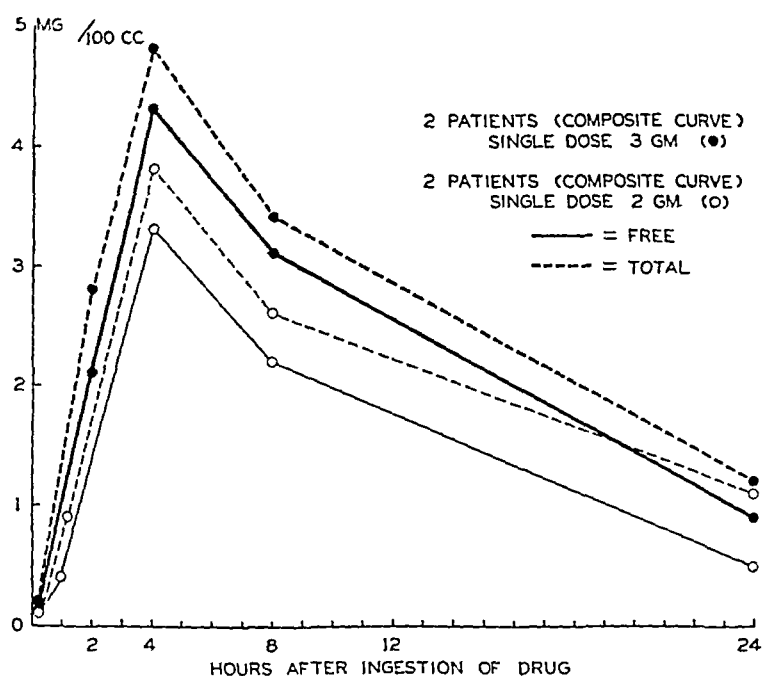


Fig 1—Concentration of sulfamethylthiazole in the blood of 4 patients after a single oral dose of the drug. Two patients received 2 Gm, and the other 2 received 3 Gm.

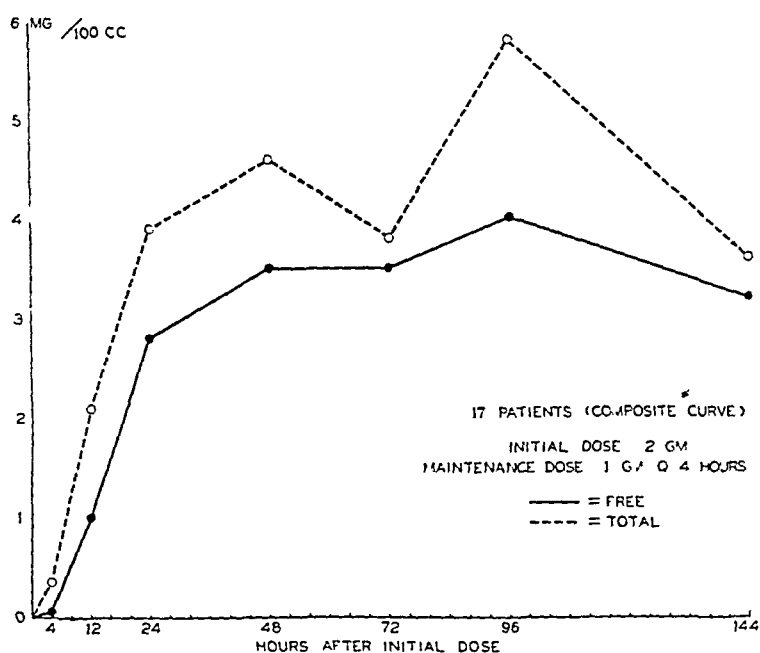


Fig 2—Concentration of sulfamethylthiazole in the blood of 17 patients who received an initial dose of 2 Gm of the drug followed by 1 Gm every four hours.

Figure 2 is a composite curve representing the concentration of sulfamethylthiazole at different intervals in the blood of 17 patients who received an initial dose of 2 Gm of the drug followed by a dose of 1 Gm

every four hours. It can be seen that the maximum rise occurred by the end of forty-eight hours, after which the level was fairly constant, ranging between 3 and 4 mg of sulfamethylthiazole per hundred cubic centimeters of blood. The drug is present in the blood largely in the free form.

In this study most of the patients received 2 Gm of the drug as the initial dose followed by 1 Gm every four hours, with resultant blood levels of 3 to 4 mg per hundred cubic centimeters, as shown in figure 1. Approximately one fourth of the patients received 3 Gm as the initial dose followed by 1.5 or 2 Gm every four hours as a maintenance dose. In the latter patients the blood levels were higher, ranging between 4.5 and 10.5 mg per hundred cubic centimeters. There did not appear to be any difference between sodium sulfamethylthiazole and sulfamethylthiazole with respect to the maximum concentration attained in the blood.

Therapeutic Value of Sulfamethylthiazole in Treatment of Pneumonia

During the period from Feb. 13 to April 1, 1940 all patients (22 in number) suffering from pneumonia who were admitted to one of the medical wards at Bellevue Hospital were given sulfamethylthiazole in addition to routine care. The first group, therefore, comprised unselected cases of pneumococcal pneumonia regardless of whether the infection was primary or secondary to some other condition. Thus, in 5 of the cases the primary condition was cardiac disease with congestive failure which preceded the onset of the pneumonia. Seventeen of the patients were over 50 years of age.

Dose—The first patients treated received 2 Gm of sulfamethylthiazole as the initial dose followed by 1 Gm every four hours. This dose was later changed to an initial dose of 3 Gm followed by 1.5 Gm every four hours, administration of the drug being maintained until there was a fall in the temperature and the pulse rate accompanied by general clinical improvement. The total dose of the drug varied from 9 to 120 Gm, the average amount of the drug used per patient was approximately 50 Gm. This exceeds the average dose of sulfapyridine employed in this service.

Alternate patients, according to the type of pneumococcus present, were scheduled, as part of a larger study of pneumonia therapy (to be published later), to receive specific rabbit serum in addition to the drug. Actually, however, only 3 received serum, since the temperature of the others fell during chemotherapy before the sputum typing was reported. Two of the patients who received serum had type II pneumococcal pneumonia without bacteremia and recovered. The third had type III pneumococcal pneumonia associated with bacteremia and died sixteen hours after admission.

Results—In 12 of the 19 patients who had pneumonia and recovered there was a crisis within twenty-four to forty-eight hours after the treatment was started. In the remainder the fall in temperature was gradual. As in the patients treated with sulfapyridine, there did not appear to be any effect on the progress of the pulmonary lesion, which ran its natural course as observed clinically and in serial roentgenograms. With the exception of delayed resolution in 3 cases and sterile pleural effusion, probably secondary to cardiac decompensation, in 2, there were no complications.

There were 5 cases of type II pneumococcic pneumonia. In these cases, in 2 of which there was associated bacteremia, there were no deaths. There were 5 cases of type III pneumococcic pneumonia, in 3 of which there was associated bacteremia, in these 5 there were 2 deaths. There was 1 case each of types V, VII and XVIII and 2 cases

TABLE 1—*Pneumonias*

Type	Distribution of Cases According to Type and Mortality Rate	
	No. of Cases	Deaths
II	5 (2*)	0
III	5 (3*)	2 (2*)
V	1	0
VII	1	0
VIII	2 (1*)	0
XVIII	1	0
Mixed	7 (1*)	1

* Pneumonia accompanied by bacteremia

of type VIII pneumococcic pneumonia. There were 7 cases of mixed infection.

In 5 of the 7 cases in which bacteremia occurred the patients recovered. One of the 2 deaths occurred within sixteen hours after the treatment was started. The patient was a 77 year old Chinese man with type III pneumococcic pneumonia who received both sulfamethylthiazole and rabbit serum. The results of cutaneous and ophthalmic tests with rabbit serum were negative, and there was no reaction after 1 cc. of serum was injected intravenously, but one hour after he had been given 40 cc. of the same serum, a shock reaction developed, accompanied by "wheezing" dyspnea, vascular collapse and death.

The other fatal case of bacteremia was that of a 71 year old man whose type III pneumococcic pneumonia accompanied by bacteremia subsided after treatment with sulfamethylthiazole. However, there was associated hypertrophy of the prostate gland accompanied by urinary retention and azotemia, and it was assumed that this factor contributed to the fatal outcome.

The third death was that of a 73 year old patient without bacteremia, who had chronic cardiac disease. He had calcareous aortitis and coronary thrombosis, as shown at autopsy. Congestive pneumonia due to the type XXIV pneumococcus developed and was treated with both serum and sulfamethylthiazole, with a fatal outcome.

THERAPEUTIC VALUE OF SULFAMETHYLTHIAZOLE IN TREATMENT OF STAPHYLOCOCCIC SEPTICEMIA

There were 5 cases of staphylococcic septicemia selected according to Kolmer's definition of this condition, "an infection of the blood by staphylococci, their pathogenic presence and products in the blood associated with infection of fixed tissues resulting in severe constitutional disturbance with the signs of sepsis." The average mortality heretofore in this infection has been approximately 80 per cent. Kolmer⁹ collected 19 cases reported in the literature in which treatment was with sulfanilamide, sulfapyridine or sulfanilyldimethylsulfanilamide (uleron) and in which there were 10 recoveries—a mortality rate of approximately 50 per cent. Baker and Shands¹⁰ recently reported the results of treatment in 103 cases of staphylococcemia, the mortality rate was 38 per cent in the group of patients who received staphylococcus antitoxin and 76 per cent in the group which did not. In the 5 cases in our series there was only 1 death. In 4 instances septicemia followed trauma to an extremity, while in the fifth it was preceded by a furuncle. The summaries of the case histories follow.

CASE 1—An 11 year old white boy was admitted to Bellevue Hospital with a history of pain in the left shoulder for eight days, following injury. On the day of his admission pain developed in the left ankle. He appeared acutely ill, and during the first week of hospitalization his temperature ranged between 103 and 105 F. On the day after admission a subpectoral abscess and an area of osteomyelitis in the lower end of the fibula were incised and drained. Cultures of the pus from both foci showed *Staphylococcus aureus haemolyticus*. Three days later another focus developed in the upper end of the right femur, which necessitated drainage.

Treatment with sulfamethylthiazole was started on the day of admission. Cultures of his blood made on the day of admission and also on the day following were positive for *Staph aureus haemolyticus*. Subsequent blood cultures were negative for the organism. A daily dose of 4 Gm., and later of 6 Gm., was given for a total of 103 Gm. It was discontinued on the appearance of gross hematuria, which then cleared in two days. His temperature gradually fell to between 99 and 100 F at the end of the third week. He remains hospitalized, two hundred and fifty-two days after admission, with the left leg in a hip spica. Improvement has been slow but constant, and no new areas of osteomyelitis have developed.

9 Kolmer, J. A. Progress in Chemotherapy of Bacterial and Other Diseases with Special Reference to the Prontosils, Sulfanilamide and Sulfapyridine, *Arch Int Med* **65** 671 (April) 1940.

10 Baker, L. D., and Shands, A. R., Jr. Acute Osteomyelitis with Staphylococcemia, *J. A. M. A.* **113** 2119 (Dec 9) 1939.

CASE 2—A 14 year old white boy was admitted to the New York Hospital Three days before admission he had been wrestling, and the following day pain developed in the left knee accompanied by chills and fever. On admission he was acutely ill, with a temperature ranging up to 105 F for the first two days. Roentgen examination showed osteomyelitis of the femur. Culture of the blood showed 5 colonies of *Staph aureus nonhaemolyticus* per cubic centimeter of blood. The following day the culture was positive on agar plates, with 1 and 4 colonies each. Five days later it was positive in the broth cultures only. Subsequent cultures were negative for the organism. Sulfathiazole was administered the first two days after admission, the total amount being 16 Gm. Since at the end of this time the septicemia persisted, treatment with sulfamethylthiazole was started. Two grams was given every four hours for a total of 110 Gm. An incision and drainage of the area of osteomyelitis of the femur were done three days after admission. At the end of eight days the temperature had fallen to normal. The boy was discharged from the hospital seven weeks after admission. The sinus tract in the hip had practically closed, and repeated roentgen examinations showed no further evidence of destruction of the bone. No toxic effect from the drug was noted.

CASE 3—A 42 year old man was admitted to the New York Hospital. Four weeks before admission a boil developed on the neck and was opened after one week. Shortly after this pain developed in the sacroiliac region, and one week before admission he had chills and fever. For the first nine days he was extremely ill, with a hectic temperature ranging between 103 and 105 F. Culture of his blood on admission was positive for *Staph aureus haemolyticus*, showing 5 colonies per cubic centimeter of blood. Four days after admission it was negative, but eight days later it was again positive, in the broth only. Subsequent cultures were negative. Treatment with sulfamethylthiazole was started two days after admission, 1 Gm being given every four hours. The use of the drug was discontinued after eight days, on the appearance of a maculopapular eruption, then resumed six days later and continued for a total dose of 86 Gm. There was no further recurrence of the rash. Twenty-six days after admission an incision and drainage of the soft tissues in the region of the twelfth thoracic vertebra yielded pus, which on culture showed *Staph aureus haemolyticus*. The patient was discharged from the hospital on July 18, walking on crutches.

CASE 4—A 47 year old man was admitted to the New York Hospital. Three and one-half months before this admission he had had a thoracotomy for acute empyema due to *Str haemolyticus*. He was followed in the clinic for dressing of the sinus tract and had made marked improvement. After one visit to the clinic he walked seventy blocks, and the next day severe pain developed in the left thigh. He was readmitted to the hospital, and one week later roentgen examination of the hip showed an acute form of destructive arthritis. Eight days after admission aspiration in the region of the left hip was done and a small amount of pus was obtained which on culture showed *Staph aureus haemolyticus*. Likewise, culture of the material draining from the old empyemic sinus tract yielded the same organism. The following day his temperature, which previously had been but little elevated, rose to 38.5 C (101.8 F) and culture of his blood was positive for *Staph aureus haemolyticus*. The following day the blood culture was negative and remained so. Treatment with sulfamethylthiazole was started immediately with doses of 1 Gm every four hours and was continued for a total of 130 Gm. Incision and drainage of the left hip were done on the thirteenth day of his stay in the hospital. Convalescence was slow and was complicated

by an abscess of the wall of the chest. He was discharged on the one hundred and fifty-seventh day of hospitalization, with the leg in fairly good condition, there was slight motion, a shortening of $\frac{3}{4}$ inch (1.8 cm) and practically no pain.

CASE 5—An 11 year old boy was admitted to the New York Hospital. Four days before admission he began to note pain in the region of a blister on his left heel. He soon became acutely ill with fever, chills and delirium. His temperature on admission was 40.3 C (104.6 F), and it ranged between 39 and 41 C (102.2 and 105.8 F) during the entire period of his hospitalization. Culture of pus from the infected blister showed *Staph aureus haemolyticus*, and culture of his blood was positive for the same organism, with 75 colonies per cubic centimeter of blood. Treatment with sulfamethylthiazole was started on admission with a dose of 2 Gm every four hours. The colonies in blood cultures were reduced to 2 per cubic centimeter four days after admission, but increased over the next six days to become innumerable. Sulfamethylthiazole was discontinued on the twelfth day of his stay in the hospital, after 98 Gm had been given. Roentgen examination of the left hip ten days after admission showed osteomyelitis, and aspiration in this region yielded pus, cultures of which also showed *Staph aureus haemolyticus*. A systolic murmur heard at the time of admission became progressively more pronounced, and petechiae appeared on the fourteenth day of his stay in the hospital. His course was progressively downhill, and he died twenty-one days after admission. Autopsy showed vegetative endocarditis of the mitral valve, acute osteomyelitis of the ilium and the sacrum, infected infarcts in the kidneys and the spleen and bronchopneumonia of all lobes accompanied by the formation of abscesses.

THERAPEUTIC VALUE OF SULFAMETHYLTHIAZOLE IN TREATMENT OF MISCELLANEOUS INFECTIONS

Pertinent data in the cases of patients with staphylococcal infections or miscellaneous infections, all of whom were treated with sulfamethylthiazole, are summarized in table 2.

In view of the small number of cases and the variety of lesions treated, it is impossible to draw any definite conclusions. However, our results were as follows:

Chemotherapy appeared effective in treating a patient with a furuncle of the upper lip and also in treating a patient with a carbuncle of the abdominal wall and septic pulmonary infarcts. Similarly, the 3 patients with cellulitis did well, especially significant was the response of the patient with cellulitis of the orbit. Of the 5 patients suffering from osteomyelitis (without bacteremia), there was a good response only in the 1 with the acute form who was treated.

In the 3 patients with pulmonary tuberculosis there was no effect, either favorable or unfavorable, on the disease, as has been the general experience with other drugs.

Of the 5 patients with bacterial endocarditis, 1 had an acute condition and died soon. Another had endocarditis due to *M. albicans* with a slowly progressive course which failed to respond to varied chemothera-

peutic agents, including sulfamethylthiazole. The other 3 patients with endocarditis had a temporary remission under the influence of the drugs, this effect being similar to that noted with sulfapyridine.

TABLE 2—*Miscellaneous Infections*

Diagnosis	No of Cases	Amount of Drug, Gm	Response	Comment
Exacerbation of chronic osteomyelitis	4	30 to 136	Variable response	No effect from sulfamethylthiazole in 2 cases, questionable beneficial effect in 2 cases
Acute osteomyelitis of os calcis after compound fracture of tibia	1	30	Recovery	Sulfamethylthiazole probably of benefit
Carbuncle on abdominal wall with septic pulmonary infarcts	1	166	Recovery	Three episodes of pulmonary infarction after surgical drainage of carbuncle, good response to therapy
Furuncle of upper lip with cellulitis of face	1	16	Recovery	Rapidly extending lesion, striking response to sulfamethylthiazole
Cellulitis of extremity	2	16 and 32	Recovery	Influence of drug on course difficult to assay
Abscess of the breast (Staphylococcus)	1	36	Recovery	Recovery not related to chemotherapy
Chronic cystitis (Staph aureus)	1	36	Improvement	Relief of symptoms, disappearance of Staph aureus, persistence of saprophytic staphylococcus
Cellulitis of orbit (Staphylococcus)	1	16	Recovery	Recovery credited to sulfamethylthiazole by ophthalmologist
Infected thoracic sinus tract (Staph aureus)	1	16	Improvement	Failure of conservative procedures before administration of drug begun
Postoperative aspiration pneumonia (Staph aureus)	1	35	Recovery	Numerous abscesses in both lungs, which later cleared, role of sulfamethylthiazole doubtful
Bronchiectasis associated with lobular pneumonia	2	16 and 26	Improvement	Subsidence of lobular pneumonia, improvement of bronchiectasis in 1 patient
Pulmonary tuberculosis	3	22, 26 and 28	No change	Institution of chemotherapy before correct diagnosis apparent
Subacute bacterial endocarditis (Streptococcus viridans)	3	22, 26 and 132	No change	Temporary remission during administration of drug
Acute bacterial endocarditis (Streptococcus alpha prime and Micrococcus tetragenus)	1	46	Death	Initial reduction in colony count, with subsequent rise
Endocarditis (Monilia albicans)	1	16	Death	No effect of sulfamethylthiazole on the course
Actinomycosis of jaw	1	156	Recovery	Complete healing of multiple sinus tracts

TOXIC REACTIONS

There were relatively few toxic reactions in this group of 53 patients, although the average amount of sulfamethylthiazole administered per patient was 52 Gm and 9 patients received over 100 Gm. Gross hematuria developed in 1 of the patients after 103 Gm of sulfamethylthiazole.

was given. However, the urine returned to normal after the use of the drug was discontinued. This patient at a later date received sulfathiazole, and after 28 Gm was given hematuria developed again. On both occasions the hematuria appeared shortly after the use of cyclopropane anesthesia, and it was considered possible that the anesthetic contributed to this complication.

It is interesting to note that 1 patient in whom hematuria and anuria developed after the taking of 6 Gm of sulfapyridine subsequently took 156 Gm of sulfamethylthiazole without any noticeable effect on the kidneys.

In 2 patients there was a mild depression of the total white cell count to 4,200 and 4,700 after doses of 166 and 26 Gm respectively of the drug. The decrease was more marked in the granular series. There was a prompt rise of the white cell count to normal in both instances after use of the drug was discontinued.

Peripheral neuropathy was encountered in 1 patient. This was in a man who had type II pneumococcic pneumonia associated with severe bacteremia (over 2,000 colonies per cubic centimeter of blood) and who received 80 Gm of the drug, with satisfactory clinical response. Paresthesias of the extremities, weakness of the limbs and ataxia developed, and he was treated with massive doses of thiamine hydrochloride and the vitamin B complex. There has been definite recession of the neuropathy (whether the recession is due to the treatment is not known), though it is too soon to tell whether there will be any permanent impairment of the peripheral nerves.

In 2 of the patients a morbilliform rash appeared in the course of treatment. This was not associated with other signs of a toxic reaction. In 1 of the patients the use of the drug was maintained with no harmful effects, and the rash disappeared spontaneously. In the other the use of the drug was discontinued temporarily but was resumed five days later, after the rash had faded. There was no reappearance of the eruption.

Nausea and vomiting occurred in 7 patients (13 per cent). The incidence of this reaction was thus uncommon, in contrast to its occurrence in approximately 50 per cent of the patients treated with sulfapyridine.

COMMENT

The final clinical evaluation of a new remedy must wait on the accumulated observations in a large number of cases. Our experience with sulfamethylthiazole has been limited to 53 cases. The results in the treatment of pneumonia compare favorably with those obtained with sulfapyridine, particularly if consideration is given to the fact that a

majority of our patients with pneumonia were over 50 years of age and nearly half of them were suffering from some associated disease which gravely affected the prognosis. The results in the 5 cases of type II pneumococcic pneumonia were especially striking, there being no deaths, though 2 of the patients had bacteremia.

The results in the cases of staphylococcic septicemia, even in this small number were encouraging in view of the usual high mortality with other methods of treatment. There was only 1 death in 5 cases. In cases of other staphylococcic infections, we believe the drug is beneficial particularly when the infection is acute. In treatment of chronic infections its value is less apparent. We treated 1 patient who had actinomycosis, and the result was so satisfactory that further trial of sulfamethylthiazole in this disease is warranted.

The drug has certain advantages and disadvantages as compared with other chemotherapeutic agents. It is better tolerated than sulfapyridine, the incidence of nausea and vomiting being low. Toxic rashes due to the drug are not common, nor have we encountered any serious effects on the red or white blood cell-forming organs. In rare instances, particularly those in which large amounts of the drug are used, a toxic peripheral neuropathy may occur. In a large number of cases reported to a manufacturer of the drug¹¹ the incidence of peripheral neuropathy has been less than 1 per cent. This side effect has in many instances been mild and has cleared up promptly. In some of these cases the neuropathy appeared as a delayed reaction some time after treatment had been terminated. In a few cases it was so severe and improvement was so slow that the manufacturers decided voluntarily to withdraw sulfamethylthiazole from clinical research. (The drug has never been made available commercially but was supplied only to selected physicians for clinical evaluation.) However, we have been so impressed with the effectiveness of sulfamethylthiazole, particularly in the treatment of staphylococcic septicemias, that we feel it is unfortunate that the possibility of peripheral neuropathy resulting from its use has necessitated its withdrawal. Nevertheless, if in the future no other drug can be shown to have the same effectiveness as sulfamethylthiazole in the treatment of staphylococcic septicemia, reconsideration of this decision might be warranted.

In the clinical trial of new derivatives of the sulfanilamide group we would reemphasize the necessity for careful watch for the early symptoms of toxic effects on the peripheral nerves. The appearance of such symptoms is an indication for immediate cessation of this therapy and the institution of antineuritic measures.

11 The Winthrop Chemical Co., Inc.

SUMMARY

Sulfamethylthiazole has been employed as a therapeutic agent in 53 cases of various types of infections. These included mainly cases of pneumonia and of staphylococcic infection. The results were favorable in the majority of cases. The most striking effect was observed in cases of pneumonia and of staphylococcic septicemia.

The toxic manifestations of sulfamethylthiazole are similar to those of other derivatives of sulfanilamide with one exception. Peripheral neuropathy, which was not noted with sulfapyridine and sulfathiazole, occurs in about 1 per cent of cases and, though infrequent, militates against the use of this drug.

Progress in Internal Medicine

LIVER AND BILIARY TRACT

A REVIEW FOR 1940

CARL H GREENE, M D

NEW YORK

As in previous reviews, no attempt has been made to give either an inclusive or a comprehensive survey of the literature dealing with diseases of the liver and the biliary tract during 1940. Instead I have selected topics that have been the subject of special advances or particular study during the year. In many cases detailed reviews have been published elsewhere, and I have referred to them instead of attempting to give a comprehensive bibliography in this article.

PORTAL HYPERTENSION AND CONGESTIVE SPLENOMEGALY— BANTI'S DISEASE

The literature dealing with the syndrome of portal hypertension and its role in the production of congestive splenomegaly and the so-called Banti syndrome has been reviewed by Greene, Plotz and Localio¹. The importance of portal hypertension in producing congestive splenomegaly has been emphasized further by Whipple² and Rousselot³. Thompson⁴ has recently summarized the experience of investigators at Presbyterian Hospital in New York and reported the results of a study of 137 cases occurring during the last ten years. One hundred of the patients have been followed over a period of years. The cases selected were those in which splenomegaly with anemia, leukopenia and thrombocytopenia were present, together with evidence of the development of an increased collateral circulation between the portal and the peripheral venous circulation. The histologic changes were characteristic.

From the Clinic for the Study of Diseases of the Liver and Biliary Tract of the Department of Medicine and the Department of Surgery, New York Post-Graduate Medical School and Hospital, Columbia University.

1 Greene, C. H., Plotz, M., and Localio, S. A. Liver and Biliary Tract. A Review for 1937, *Arch Int Med* **61** 655 (April) 1938.

2 Whipple, A. O. The Medical-Surgical Splenopathies, *Bull New York Acad Med* **15** 174 (March) 1939.

3 Rousselot, L. M. Congestive Splenomegaly (Banti's Syndrome), *Bull New York Acad Med* **15** 188 (March) 1939.

4 Thompson, W. P. The Pathogenesis of Banti's Disease, *Ann Int Med* **14** 255 (Aug.) 1940.

Thompson ⁴ reports that in this group of cases the splenomegaly, the collateral circulation and the esophageal varices result from portal hypertension in the presence of a normal peripheral venous pressure. This portal hypertension is the common denominator in all cases of the Banti syndrome. A simple mechanical cause for the portal hypertension was found in every case that was adequately studied. Thompson and his associates observed that the hepatic scarring seen in cases of prolonged schistosomiasis resulted in the greatest increase in portal pressure and the largest spleens. Periportal cirrhosis of the Laennec type resulted in a variable degree of splenomegaly. Pathologic studies showed that in about 60 per cent of the cases of periportal cirrhosis there was considerable distortion of the vascular bed within the liver, with only minimal evidence of parenchymal injury. In the majority of these cases the patients died from hemorrhage due to rupture of esophageal varices. In the remaining 40 per cent of the cases of periportal cirrhosis, there was less distortion of the vascular bed within the liver but there was evidence of injury to the parenchyma. The patients in these cases died in coma from hepatic failure. Obstructive biliary fibrosis and cardiac fibrosis of the liver usually did not produce splenomegaly. Hepatic cirrhosis was found in 68 per cent of the cases. When not present at the time of splenectomy it did not develop subsequently.

In the remaining cases the congestive splenomegaly was due to a variety of causes, especially to thrombosis of the portal or splenic vein and to the so-called cavernous transformation of the portal vein. In 4 children the portal hypertension was found to be due to a stenosis of the portal vein. The histopathologic changes in the spleen were the same in all cases irrespective of the lesions producing the portal obstruction. Thompson therefore suggests that the terms Banti's disease and splenic anemia be replaced by congestive splenomegaly.

A different conception of the Banti syndrome has recently been discussed in detail by Ravenna ⁵. He admits that in many cases congestive splenomegaly is associated with evidence of circulatory obstruction and increased pressure in the splenic vein. On the other hand, he points out that there are many cases in which the obstructive factor is missing but the signs of portal hypertension nevertheless are present. Ravenna believes that this apparent contradiction may be explained on the basis of an increased flow of blood into the spleen. He concludes, therefore, that in these cases the condition is to be considered as due to an active, primary splenic congestion and not to a passive congestion, secondary to portal obstruction.

5 Ravenna, P. Banti Syndrome (Fibrocongestive Splenomegaly). Definition, Classification and Pathogenesis, *Arch Int Med* 66: 879 (Oct) 1940.

Ravenna reviews the literature in detail and in support of his views points out the following facts 1 The inflow of blood to the splenic pulp is regulated chiefly by the malpighian arteries and by the other arteries in the pulp and trabeculae The contraction of these vessels has been shown to be capable of obliterating their lumen 2 The output of splenic blood is limited by the peripheral resistance of the liver, which normally is small When the splenic outflow increases above a definite amount, however, the portal pressure must rise 3 Lesions of the malpighian and other small arteries, especially periarteriolar hemorrhage and periarteriolar fibrosis, are constantly present, even in the early stages of Banti's syndrome He considers

This last point gives enough evidence to warrant the assumption that the small splenic arteries are the seat of early lesions In consequence, their function of adjusting the intake of blood is altered, and blood enters the spleen in an increased quantity, which cannot be discharged through the hepatic resistance under normal conditions Thus, the spleen becomes congested and widens, the elastic tension of the supporting framework increases, raising the pressure of the outflowing blood This condition permits an increased amount of blood to pass through the small hepatic vessels

The splenohepatic circulation, altered in consequence of the insufficient regulating function of diseased splenic arterioles, is subject to a compensatory rise of venous pressure, which is a direct result of the splenic dilatation

Becoming chronic, the splenic engorgement may be directly responsible for some lesions of the splenic pulp (fibrosis or hyperplasia), while the venous hypertension causes dilatation of splenic and portal veins and, eventually, their thrombosis Further consequences are degenerative changes in the liver cells, which may not be extraneous to the genesis of portal cirrhosis

Subsequently, either splenic thrombosis or cirrhosis of the liver, or both together, aggravate the portal congestion and may dominate the further development of the disease They are complications or associated morbid conditions and not the first cause of the congestion, because—as should always be remembered—splenic congestion may be found independent of either

Obviously, the favorable effect of splenectomy or of ligation of the splenic artery, which often, besides relieving the general and hematologic conditions, diminishes the tendency to gastroesophageal hemorrhages and ascites, is due to the removal of the primary cause of portal congestion But some failure, often cited in the literature, should have been foreseen, as splenectomy cannot remove the eventual thrombosis or the cirrhosis, nor can it always modify the state of gastroesophageal varices or of the widespread dilatation of submucous and subserous small vessels of the esophagus and the stomach, which is frequently seen in cases of this kind

The human spleen should be considered as an elastic rather than as a contractile organ Its variations in size depend on variations in the volume of the inflowing blood, rather than on active contractions of the smooth muscle of its supporting framework

From a mechanical point of view, the spleen might be defined as an automatic controller which regulates the pressure of the splenic venous blood in order to maintain the balance between the volume of inflowing blood and the amount which can be discharged through the hepatic resistance Normally, and

within certain limits, in pathologic conditions the splenic elasticity guarantees a pressure sufficient to secure the further progress of venous portal blood. Congestive splenic enlargement is therefore a mechanism to counterbalance either increased volume of portal blood or increased peripheral resistance to the discharge of a normal amount of blood.

Interesting as is Ravenna's assumption, the discrepancies between it and the "reservoir function" of the spleen described by Barcroft and cited in present day textbooks of physiology⁶ must be kept in mind. The need for a pressure regulator in the portal system is difficult to explain on a teleologic basis, but teleologic reasoning often is faulty. Of the cases of Banti's syndrome I have seen, there were many in which there was no apparent correlation between the size of the spleen and the clinical evidence of portal hypertension. This review by Ravenna is thought provoking, and it is to be hoped that it will stimulate further study in an obscure field of medicine.

VITAMIN K AND BLOOD COAGULATION

The story of vitamin K in its relation to blood coagulation has now been completed in many of its details. There were two main lines of development. On the one hand, there were the early recognition of the hemorrhagic tendency of patients with obstructive jaundice or biliary fistulas and the gradual recognition that the likelihood of bleeding increased with the length of time and completeness with which bile was excluded from the intestine. Transfusion or the administration of bile served to diminish the danger of hemorrhage but was not curative. Finally, there came the demonstration that the tendency to hemorrhage was due to a diminution in the prothrombin content of the blood plasma.

On the other hand, there was the observation that when chicks were placed on a low fat diet a hemorrhagic disease developed. This was shown to be a specific avitaminosis, and the antihemorrhagic factor was designated as vitamin K (*koagulations vitamin*). It was further shown that the hemorrhagic disease of chicks was due to hypoprothrombinemia and that the latter could be cured by the feeding of extracts of alfalfa or putrefied fish meal. These extracts were equally effective in treating the hypoprothrombinemia of jaundiced patients.

The purification of vitamin concentrates led shortly to the crystallization of vitamin K₁ and the elucidation of its chemical structure as 2-methyl-3-phytyl-1, 4-naphthoquinone. Furthermore, it was established that many other quinone compounds possessed physiologic properties analogous to those of vitamin K. Of these, the compound 2-methyl-1, 4-naphthoquinone (now known as menadione) was found to be even more active than the natural vitamin K₁. This story has been reported

⁶ Best, C. H., and Taylor, N. B. *The Physiological Basis of Medical Practice*, Baltimore, William Wood & Company, 1937.

in detail in previous reviews in the ARCHIVES,⁷ as well as in recent reviews by Snell and Butt,⁸ Dam,⁹ Feigelson,¹⁰ Brinkhous,¹¹ Almquist¹² and Andrus¹³ The extent of the literature is readily judged from the 264 articles cited in the review of Brinkhous

Extensive clinical studies have amplified the knowledge of hypopiothrombinemia and of deficiency of vitamin K It is now recognized that hypoprothrombinemia which responds to the therapeutic use of preparations of vitamin K may occur under the following circumstances

1 From the prolonged use of diets (usually low in fat) which are deficient in vitamin K Fortunately, while cases of this type have been described in human beings,¹⁴ they are rare

2 In newborn infants A number of investigators have found that a reduction in the prothrombin content of the plasma was present in newborn infants or developed during the first few days of life Extreme hypoprothrombinemia seems to be the rule in cases of hemorrhagic diseases of the newborn¹⁵ In such cases the response to either oral or

7 Greene, C H, and Hotz, R Liver and Biliary Tract A Review for 1938, Arch Int Med **63** 778 (April) 1939 Greene, C H, and Farrell, E Liver and Biliary Tract A Review for 1939, *ibid* **65** 847 (April) 1940

8 Snell, A M Vitamin K Its Properties, Distribution and Clinical Importance, a Preliminary Report, J A M A **112** 1457 (April 15) 1939 Snell, A M, and Butt, H R Supplementary Report on Vitamin K, *ibid* **113** 2056 (Dec 2) 1939

9 Dam, H Fat-Soluble Vitamins, in Luck, J M, and Smith, J H C Annual Review of Biochemistry, Stanford University, Calif, Stanford University Press, 1940, vol 9, p 353

10 Ferguson, J H Blood Coagulation, Biophysical Characters, and Formed Elements, in Luck, J M, and Hall, V E Annual Review of Physiology, Stanford University, Calif, Stanford University Press, 1940, vol 2, p 71

11 Brinkhous, K M Plasma Prothrombin Vitamin K, Medicine **19** 329 (Sept) 1940

12 Almquist, H J Vitamin K, Physiol Rev **21** 194 (Jan) 1941

13 Andrus, W DeW The Newer Knowledge of Vitamin K, Bull New York Acad Med **17** 116 (Feb) 1941

14 Kark, R, and Lozner, E L Nutritional Deficiency of Vitamin K in Man, Lancet **2** 1162 (Dec 2) 1939

15 Brinkhous, K M, Smith, H P, and Warner, E D Plasma Prothrombin Level in Normal Infancy and in Hemorrhagic Disease of the Newborn, Am J M Sc **193** 475 (April) 1937 Waddell, W W, Jr, and Guerry, Du P, III Effect of Vitamin K on the Clotting Time of the Prothrombin and the Blood with Especial Reference to Unnatural Bleeding of the Newborn, J A. M. A **112** 2259 (June 3) 1939 Quick, A J, and Grossman, A M The Nature of the Hemorrhagic Disease of the Newborn Delayed Restoration of the Prothrombin Level, Am J M Sc **199** 1 (Jan) 1940 Nygaard, K K Prophylactic and Curative Effect of Vitamin K in Hemorrhagic Disease of the Newborn (Hypoprothrombinemia Hemorrhagica Neonatorum), Acta obst et gynec Scandinav

parenteral therapy with vitamin K is good. It is more important that the condition can be prevented by the administration of the vitamin to the mother prior to delivery.¹⁶

3 From inadequate absorption from the intestine as a result of diarrheal diseases, such as chronic ulcerative colitis, regional enteritis or sprue.¹⁷ Intestinal fistulas, by short-circuiting part of the bowel, may have the same effect. The hypoprothrombinemia in cases of such diseases may be so severe as to produce serious hemorrhage (in 6 of 57 cases reported by Mackie), but it responds well to therapy with vitamin K.¹⁸ Because of the uncertainty of intestinal absorption, the parenteral administration of 2-methyl-1, 4-naphthoquinone would seem to be particularly desirable in such cases.

4 From inadequate absorption from the intestine in the absence of bile, due to (a) obstruction to the bile ducts from any cause, (b) the exclusion of bile by an external biliary fistula or (c) a deficient secretion of bile salts by the liver. Because of the absence of bile salts from the intestine and the resultant digestive disturbances, vitamin K is not absorbed, so that hypoprothrombinemia and deficiency of vitamin K occur most frequently and are most pronounced under these conditions. When the prothrombin falls to a critical level, usually about 20 per cent

19 361, 1939 Owen C A, Hoffman, G R, Ziffren, S E, and Smith, H P. Blood Coagulation During Infancy, *Proc Soc Exper Biol & Med* **41** 181 (May) 1939. Poncher, H G, and Kato, K. Treatment of Hypoprothrombinemia Haemorrhagica Neonatorum (Hemorrhagic Disease of the Newborn) with Vitamin K, *J A M A* **115** 14 (July 6) 1940.

16 Hellman, L M, and Shettles, L B. Factors Influencing Plasma Prothrombin in the Newborn Infant. I Prematurity and Vitamin K, *Bull Johns Hopkins Hosp* **65** 138 (July) 1939. Shettles, L B, Delfs, E, and Hellman, L M. Factors Influencing Plasma Prothrombin in the Newborn Infant. II Antepartum and Neonatal Ingestion of Vitamin K Concentrate, *ibid* **65** 419 (Nov) 1939. MacPherson, A I S, McCallum, E, and Haultain, W F T. Effect of Intra-Partum and Neonatal Administration of Synthetic Vitamin K Analogues on the Newborn, *Brit M J* **1** 839 (May 25) 1940.

17 (a) Butt, H R, Snell, A M, and Osterberg, A E. The Use of Vitamin K and Bile in Treatment of the Hemorrhagic Diathesis in Cases of Jaundice, *Proc Staff Meet, Mayo Clin* **13** 74 (Feb 2) 1938, (b) Further Observations on the Use of Vitamin K in the Prevention and Control of the Hemorrhagic Diathesis in Cases of Jaundice, *ibid* **13** 753 (Nov 30) 1938. (c) Clark, R L, Jr, Dixon, C F, Butt, H R, and Snell, A M. Deficiency of Prothrombin Associated with Various Intestinal Disorders. Its Treatment with the Antihemorrhagic Vitamin (Vitamin K), *ibid* **14** 407 (June 28) 1939. (d) Mackie, T T. Vitamin K Deficiency in the Absence of Jaundice, *New York State J Med* **40** 897 (July 1) 1940. (e) Allen, J G. The Comparative Prothrombin Responses to Vitamin K and Several of Its Substitutes in a Case of Non-Tropical Sprue, *New England J Med* **224** 195 (Jan 30) 1941. (f) Kark, R, Souter, A W, and Hayward, J C. A Haemorrhagic Diathesis in Idiopathic Steatorrhoea. Observations on Its Association with Vitamin K Deficiency, *Quart J Med* **9** 247 (Oct) 1940.

18 Mackie^{17d} Allen^{17e} Kark, Souter and Hayward^{17f}

of normal, bleeding occurs. Postoperative bleeding is particularly common, for it has been shown that the necessary manipulation of the liver may cause a significant postoperative reduction in the prothrombin content of the plasma. If the liver is still functionally active, there is good response to the therapeutic administration of vitamin K under such circumstances. Vitamin K and bile salts may be given orally, or crystalline quinone derivatives, such as 2-methyl-1, 4-naphthoquinone,¹⁹ may be injected.

5. Injury to the liver. A normally functioning liver is necessary for the maintenance of a normal level of prothrombin in the plasma.²⁰ Dramatic as is the effect of vitamin K on blood coagulation in vivo, it is without demonstrable effect in vitro.¹¹ Present evidence indicates that prothrombin arises in the liver and that the liver is the chief, if not the only, site of formation of this substance. Injury to the liver by chloroform,²¹ by partial extirpation²² or even by operative massage²³ causes a decrease in the prothrombin in the plasma. Total hepatectomy produces rapid and progressive development of hypoprothrombinemia.²⁴ Most important is the fact that after hepatectomy the administration of vitamin K no longer causes an increase in the prothrombin.

Clinically, it has also been observed that hypoprothrombinemia is frequently seen in association with primary hepatic disease, such as cirrhosis, atrophy or chronic hepatitis. Patients with such disease, if the hepatic injury is sufficiently severe, will not respond even to injection of large doses of vitamin K.²⁵ In consequence, several authors have

19 Stewart, J. D. Prothrombin Deficiency and Effects of Vitamin K in Obstructive Jaundice and Biliary Fistula, *Ann Surg* **109** 588 (April) 1939.
Townsend, S. R., and Mills, E. S. Hemorrhagic Tendency Associated with Prothrombin Deficiency and Its Treatment with Vitamin K and Bile, *Canad. M. A. J.* **42** 541 (June) 1940.

20 Andrus, W. D., and Lord, J. W., Jr. Clinical Investigations of Some Factors Causing Prothrombin Deficiency. Significance of the Liver in Their Production and Their Correction, *Arch Surg* **41** 596 (Sept.) 1940.

21 Smith, H. P., Warner, E. D., and Brinkhous, E. D. Prothrombin Deficiency and the Bleeding Tendency in Liver Injury (Chloroform Intoxication), *J. Exper. Med.* **66** 801 (Dec.) 1937.

22 Warner, E. D. Plasma Prothrombin. Effect of Partial Hepatectomy, *J. Exper. Med.* **68** 831 (Dec.) 1938.

23 Lord, J. W., Jr. The Effect of Trauma of the Liver on the Plasma Prothrombin. An Experimental Study, *Surgery* **6** 896 (Dec.) 1939.

24 Warren, R., and Rhoads, J. E. The Hepatic Origin of the Plasma Prothrombin. Observations After Total Hepatectomy in the Dog, *Am. J. M. Sc.* **198** 193 (Aug.) 1939. Andrus, W. D., Lord, J. W., Jr., and Moore, R. A. The Effect of Hepatectomy on the Plasma Prothrombin and the Utilization of Vitamin K, *Surgery* **6** 899 (Dec.) 1939.

25 (a) Butt, H. R., Snell, A. M., and Osterberg, A. E. The Pre-Operative and Post-Operative Administration of Vitamin K to Patients Having Jaundice,

suggested that the character of the response to parenterally administered vitamin K may be used as a test of hepatic function

Methods of Administration—The initial clinical reports dealt with the use of vitamin K concentrates prepared from alfalfa or from putrefied fish meal. Such preparations had to be given by mouth with bile salts added to facilitate absorption. The present trend seems to be toward the use of the synthetic preparations, especially 2-methyl-1, 4-naphthoquinone²⁶. This has been given by mouth in doses of from 2 to 10 mg daily. It may be given intramuscularly in doses of 1 to 2 mg dissolved in oil or injected intravenously dissolved in physiologic solution of sodium chloride. The parenteral route of administration seems particularly indicated when a rapid effect is essential or when response to oral therapy has been absent or unsatisfactory. A variety of active synthetic compounds have been described, but it is still too soon to draw final conclusions regarding a choice among them in therapy.²⁷

RELATION OF VITAMIN A TO THE LIVER

The recent studies on vitamin K have shown not only that bile is essential for its absorption but that after absorption it cannot be utilized by a damaged liver. This has stimulated interest in the behavior of

J A M A **113** 383 (July 29) 1939 (b) Stewart, J D, and Rourke, G M. Control of Prothrombin Deficiency in Obstructive Jaundice by Use of Vitamin K, *ibid* **113** 2223 (Dec 16) 1939 (c) Pohle, F J, and Stewart, J K. Observations on the Plasma Prothrombin and the Effects of Vitamin K in Patients with Liver or Biliary Tract Disease, *J Clin Investigation* **19** 365 (March) 1940 (d) Scanlon, G H, Brinkhous, K M, Warner, E D, Smith, H P, and Flynn, J E. Plasma Prothrombin and the Bleeding Tendency with Special Reference to Jaundiced Patients and Vitamin K Therapy, *J A M A* **112** 1898 (May 13) 1939 (e) Bollman, J L, Butt, H R, and Snell, A M. The Influence of the Liver on the Utilization of Vitamin K, *ibid* **115** 1087 (Sept 28) 1940 (f) Smith, H P, Ziffren, E E, Owen, C A, and Hoffman, G R. Clinical and Experimental Studies on Vitamin K, *ibid* **113** 380 (July 29) 1939 (g) Wilson, S J. Quantitative Prothrombin and Hippuric Acid Determinations as Sensitive Reflectors of Liver Damage in Human Subjects, *J Lab & Clin Med* **25** 1139 (Aug) 1940 (h) Andrus¹³

26 Andrus, W DeW, and Lord, J W, Jr. Correction of Prothrombin Deficiencies by Means of 2-Methyl-1, 4-Naphthoquinone Injected Intramuscularly, *J A M A* **114** 1336 (April 6) 1940 Cheney, G. The Clinical Value of Vitamin K, *ibid* **115** 1082 (Sept 28) 1940 Allen, J G, and Julian, O C. Clinical Use of a Synthetic Substance Resembling Vitamin K (2-Methyl-1, 4-Naphthoquinone), *Arch Surg* **40** 912 (May) 1940 Norcross, J W, and McFarland, M D. Intravenous Use of 2-Methyl-1,4-Naphthoquinone in Hypoprothrombinemia, *J A M A* **115** 2156 (Dec 21) 1940

27 Anderson, E R, Karabin, J E, Udetsky, H, and Seed, L. Parenteral Administration of a Water-Soluble Compound with Vitamin K Activity. 4-Amino-2-Methyl-1-Naphthol Hydrochloride, *Arch Surg* **41** 1244 (Nov) 1940

the other vitamins. The early experiments of Greaves and Schmidt²⁸ suggested that vitamin A was absorbed even though there was complete biliary obstruction. Altschule,²⁹ on the other hand, reported evidence of a deficiency of vitamin A in patients with complete biliary obstruction due to congenital atresia of the ducts.

More recently, Breese and McCoord,³⁰ in a study of a series of children with so-called catarrhal jaundice, used chemical methods to determine the absorption of vitamin A into the blood. During the first nine days of the disease the majority of the children showed deficient absorption of vitamin A, but after the tenth day the absorption curve was normal. When absorption was delayed, the administration of bile salts usually sufficed to produce normal absorption curves.

Night blindness is one of the earliest and most constant manifestations of a deficiency of vitamin A in adults. Photometric measurement of the dark adaptation of the eye affords a method of recognizing and studying this effect of vitamin A deficiency. The early reports of Jeghers³¹ have been amplified by Haig, Hecht and Patek,³² Zaffke,³³ Patek and Haig³⁴ and Wohl and Feldman.³⁵

There are many factors besides hepatic injury which contribute to the development of a deficiency of vitamin A. The aforementioned reports show that such a deficiency can be demonstrated in patients with hepatic disease. This is true in cases of hepatic disease with jaundice but is even more apparent in cases of cirrhosis without jaundice. In

28 Greaves, J. D., and Schmidt, C. L. A. On the Absorption and Utilization of Carotene and Vitamin A in Choledochocolonostomized Vitamin A Deficient Rats, *Am J Physiol* **111** 492 (April) 1935, The Utilization of Carotene by Jaundiced and Phosphorus Treated Vitamin A Deficient Rats, *ibid* **111** 502 (April) 1935.

29 Altschule, M. D. Vitamin A Deficiency in Spite of Adequate Diet in Congenital Atresia of Bile Ducts and Jaundice, *Arch Path* **20** 845 (Dec.) 1935.

30 Breese, B. B., and McCoord, A. B. Vitamin A Absorption in Catarrhal Jaundice, *J Pediat* **16** 139 (Feb.) 1940.

31 Jeghers, H. Night Blindness as a Criterion of Vitamin A Deficiency. Review of the Literature with Preliminary Observations on the Degree and Prevalence of Vitamin A Deficiency Among Adults in Both Health and Disease, *Ann Int Med* **10** 1304 (March) 1937.

32 Haig, C., Hecht, S., and Patek, A. J., Jr. Vitamin A and Rod-Cone Dark Adaptation in Cirrhosis of the Liver, *Science* **87** 534 (June 10) 1938.

33 Zaffke, K. H. Night Blindness as a Symptom of Thyrotoxicosis and of Hepatic Diseases, *Deutsches Arch f klin Med* **183** 433, 1939.

34 Patek, A. J., Jr., and Haig, C. Occurrence of Abnormal Dark Adaptation and Its Relation to Vitamin Metabolism in Patients with Cirrhosis of the Liver, *J Clin Investigation* **18** 609 (Sept.) 1939.

35 Wohl, M. G., and Feldman, J. B. Vitamin A Deficiency in Diseases of the Liver. Its Detection by Dark Adaptation Method, *J Lab & Clin Med* **25** 485 (Feb.) 1940.

cases of cirrhosis, Patek and Haig³⁴ were able to show that the deficiency was not attributable to an inadequate intake of the vitamin in the food. The parenteral injection of vitamin A in cases of cirrhosis improves the dark adaptation, but the rate of improvement is much slower than that seen in cases of dietary deficiency. This observation suggests that in cases of cirrhosis or severe hepatic damage there is a disturbance in the intermediary metabolism and utilization of vitamin A.

LEPTOSPIROSIS ICTEROHAEMORRHAGICA

Sporadic cases of Weil's disease continue to be reported with increasing frequency. Tokuyama³⁶ reports 12 cases seen in Hawaii between 1927 and 1932 and emphasizes the complete clinical and bacteriologic identity with those occurring in Japan. Keay³⁷ reports that he has seen more than 40 cases in Hawaii since 1928. Blake³⁸ records a case in Connecticut, and Haschec and Tobey,³⁹ 1 in New Jersey. Havens, Bucher and Reimann⁴⁰ recognized a small epidemic (7 cases) affecting bathers in an infected stream near Philadelphia. Early recognition is essential, for, as pointed out, the early administration of immune serum of high titer is of prime importance in treatment. Such serum is not available commercially in the United States at present, it is of interest, therefore, that Keay reports equally spectacular improvement after the transfusion of 500 cc of whole blood from a donor who had recovered from the disease.

Learn⁴¹ reports a series of 62 cases of acute infectious jaundice seen in Pennsylvania between 1937 and 1939. Children were predominantly infected, though the ages varied, the youngest patient being 3 and the oldest 47. Clinical evidence suggested that the disease was transmitted from person to person and that most adults were immune. *Leptospira* were isolated in a sufficient number of cases to be considered the causal organisms. Careful studies in the past have failed to demonstrate an etiologic relationship between *Leptospira icterohaemorrhagica* and

36 Tokuyama, S. Weil's Disease (*Leptospira Icterohaemorrhagiae*) in Hawaii. Its Serum Treatment, *J A M A* **114** 2195 (June 1) 1940.

37 Keay, T. Infectious Jaundice in Hawaii, *J A M A* **110** 110 (Jan 15) 1938.

38 Blake, F. G. Weil's Disease in the United States. Report of a Case in Connecticut, *New England J Med* **223** 561 (Oct 10) 1940.

39 Haschec, W., and Tobey, F. L. A Case of Weil's Disease, *J A M A* **113** 1319 (Sept 30) 1939.

40 Havens, W. P., Bucher, C. J., and Reimann, H. A. Leptospirosis. A Public Health Hazard, Report of a Small Outbreak of Weil's Disease in Bathers, *J A M A* **116** 289 (Jan 25) 1941.

41 Learn, B. G. Clinical Report of Epidemic of Acute Infectious Jaundice, Pennsylvania. *M J* **44** 18 (Oct) 1940.

epidemic infectious jaundice. Harmless leptospiras occur in nature, so it is questionable if their presence in these cases can be considered significant.

Norton⁴² reports a similar epidemic of jaundice involving 23 cases which he observed in Nevada. In the majority of cases the transmission seemed to be by contact. The average incubation period was thirty-one days. Agglutination tests negative for *Leptospira* served to rule out Weil's disease. Comparison of these findings with foreign reports, such as that of Bloch,⁴³ indicates the similarity of the epidemics of infectious jaundice in Europe and America. Lainer⁴⁴ tried, without success, to demonstrate the causal organism in cases of sporadic catarrhal jaundice. In 15 cases, 300 cc of blood from a jaundiced patient was transfused into a healthy subject. Bile obtained by duodenal drainage was also given to healthy subjects. No evidence of hepatitis or of jaundice developed in any of them. Lainer expressed the belief that these negative results served to exclude the effect of a specific icterogenic organism in producing catarrhal jaundice. Whether equally negative results would be obtained in the course of an epidemic of catarrhal jaundice remains to be proved.

HEPATIC FUNCTION IN HYPERTHYROIDISM

That the liver may be affected in cases of hyperthyroidism has long been known. Jaundice is recognized as a serious and usually late development in the crisis of exophthalmic goiter. Experimental studies have shown that the feeding of thyroid to animals results in almost complete disappearance of glycogen from the liver. This has been variously described as due either to a failure of glycogen deposition or to an increased glycogenolysis. Tests of hepatic function have shown changes in cases of hyperthyroidism. This subject has recently been discussed in a comprehensive report by Lichtman,⁴⁵ who gives a particularly good historical review of the literature. He points out the difficulties in such a study and the confusion arising from the fact that jaundice and hepatic changes may result from circulatory disturbances, cholangitis or hepatitis independently of the effects of hyperthyroidism. Serious jaundice, fortunately, is rare in cases of exophthalmic goiter, but still it occurs. The pathologic lesions resolve themselves into three main types (1)

42 Norton, J. A. Acute Infectious Jaundice, *J. A. M. A.* **113** 916 (Sept. 2) 1939.

43 Bloch, W. Epidemic Appearance of Catarrhal Icterus, *Schweiz. med. Wchnschr.* **69** 445 (May 20) 1939.

44 Lainer, F. Question of Infectiousness of Icterus, *Wien. klin. Wchnschr.* **53** 601 (July 26) 1940.

45 Lichtman, S. S. Liver Function in Hyperthyroidism with Special Reference to the Galactose Tolerance Test, *Ann. Int. Med.* **14** 1199 (Jan.) 1941.

acute degenerative lesions with fatty changes and necrosis or even acute yellow atrophy, (2) more chronic lesions appearing as subacute atrophy, and (3) cirrhosis or chronic fibrosis of the liver

While serious jaundice is rare in cases of hyperthyroidism, studies of tests of hepatic function indicate that in 45 to 90 per cent of such cases there is some evidence of functional disturbance. The value of the hippuric acid test in cases of hyperthyroidism has been stressed by Bartels and Perkin⁴⁶ and by Bartels⁴⁷ in a report of 148 cases. They report a correlation of the excretion of hippuric acid with the basal metabolic rate and the cholesterol content of the blood in cases of untreated hyperthyroidism. The hippuric acid excretion improved with preoperative preparation, and in the great majority of cases values were normal three months after operation. Haines, Magath and Power⁴⁸ repeated these studies in a series of 78 cases of hyperthyroidism. They confirmed the previous finding of a reduction in the excretion of hippuric acid in a significant percentage of cases. They also found a slight correlation between the excretion of hippuric acid and the basal metabolic rate. Haines, Magath and Power, however, do not agree with Bartels⁴⁷ and Boyce and McFetridge,⁴⁹ but feel that the test cannot be given a position of importance in the handling of patients with hyperthyroidism. They consider that clinical judgment of visceral damage and increased surgical risk is reasonably accurate and more satisfactory than any single laboratory test. They therefore question the clinical value of the hippuric acid test in the management of patients with hyperthyroidism.

Lichtman, in his own observations, stresses the value of the galactose tolerance test. He found, as did MacLagan and Rundle,⁵⁰ that galactose tolerance was reduced in cases of thyrotoxicosis. It improved with administration of iodine, and the greatest proportion of normal values were obtained after thyroidectomy. Lichtman considers the basic functional disturbance in the liver in cases of hyperthyroidism to be associated with carbohydrate metabolism and reports that the galactose tolerance test is the most satisfactory one for determining hepatic function.

46 Bartels, E. C., and Perkin, H. J. Liver Function in Hyperthyroidism as Determined by the Hippuric Acid Test, *New England J. Med.* **216** 1051 (June 17) 1937

47 Bartels, E. C. Liver Function in Hyperthyroidism as Determined by the Hippuric Acid Test, *Ann. Int. Med.* **12** 652 (Nov.) 1938

48 Haines, S. F., Magath, T. B., and Power, M. H. The Hippuric Acid Test in Hyperthyroidism, *Ann. Int. Med.* **14** 1225 (Jan.) 1941

49 Boyce, F. F., and McFetridge, E. M. Studies in Liver Function by the Quick Hippuric Acid Test. II. Thyroid Disease, *Arch. Surg.* **37** 427 (Sept.) 1938

50 MacLagan, N. F., and Rundle, F. F. Liver Function in Thyrotoxicosis, *Quart. J. Med.* **9** 215 (July) 1940

The exact mechanism of the functional disturbance in the liver in hyperthyroidism is not understood, but Lichtman suggests that glycogen depletion is a necessary result of the metabolic demands of the hyperthyroid state. Not only are the carbohydrate stores exhausted, but the protein stores are depleted. These changes need not produce functional disturbances, but they deprive the liver of its prime protective agents and leave it susceptible to damage by thyroxin, toxic products of endogenous intermediary metabolism, bacterial toxins or the like. There has been a tendency to stress the role of the liver in the development of the clinical picture of thyroid crisis. Some authors go so far as to ascribe the mortality in cases of such conditions to "liver deaths"⁵¹. This topic has been clarified by the report of Foss, Hunt and McMillan⁵² on a series of 96 deaths from thyroid disease. Postmortem examinations were made in 29 cases. Death in 9 of the latter was due to associated conditions rather than to the thyroid disease. In 9 other cases in which a clinical diagnosis of thyroid crisis was made, the autopsy revealed that death really was due to an overwhelming infection which antedated the symptoms of crisis. Only 11 of the 29 cases in which autopsy was done could rightfully be considered as examples of true thyroid crisis. In these cases the pathologist was unable to explain the pathogenesis of the crisis. There were varying degrees of hepatic necrosis, but Foss and his associates were unable to find any correlation between the degree of injury to the liver and the degree of toxemia. They conclude, therefore, that in cases of thyroid crisis neither the heart, liver, thyroid nor thymus alone seems to be at fault and that the mechanism of this condition is as yet but little understood.

CAUSES OF DEATH IN CASES OF HEPATIC DISEASE

Unfavorable symptoms often appear acutely in cases of hepatic disease. These may lead to the death of the patient in a few days. Descriptions by the master clinicians of the past of the course and clinical

51 Lahey, F. H. Reduction of Mortality in Hyperthyroidism, *New England J. Med.* **213** 475 (Sept 5) 1935. Frazier, W. D., and Freiman, H. Alteration in Liver Glycogen Following Thyroid, Iodine and Glucose Feeding, *Surg., Gynec. & Obst.* **60** 27 (Jan) 1935. Frazier, C. H., and Brown, R. B. The Thyroid and Liver, *Tr. Am. A. Study Goiter*, 1935, pp 168-178. Lahey, F. H. Stage Operations in Severe Hyperthyroidism, *Ann. Surg.* **104** 961 (Dec) 1936. Dinsmore, R. S. Factors Influencing Morbidity in Thyroid Surgery, *J. A. M. A.* **109** 179 (July 17) 1937. Maes, U., Boyce, F. F., and McFetridge, E. M. Further Observations of Thyroid Disease in a Nonendemic Area, *Ann. Surg.* **105** 700 (May) 1937. Bartlett, W., Jr. Role of the Liver in Thyrotoxicosis, *Surgery* **3** 261 (Feb) 1938. Shaffer, J. M. Diseases of the Liver in Hyperthyroidism, *Arch. Path.* **29** 20 (Jan) 1940.

52 Foss, H. L., Hunt, H. F., and McMillan, R. M. The Pathogenesis of Crisis and Death in Hyperthyroidism, *J. A. M. A.* **113** 1090 (Sept 16) 1939.

picture presented in such cases cannot be improved on at present. The study of postoperative deaths by surgeons has also led to the accumulation of an extensive literature dealing with various types of so-called liver death.

Hypoglycemia—The first cleancut experimental picture of hepatic insufficiency was that which Mann⁵³ produced by the removal of the liver in dogs. Mann showed that the acute collapse of the dogs was associated with a reduction in the blood sugar level and that the animals could be revived by the administration of dextrose. These studies and those of Fischler⁵⁴ provided the experimental basis for the recognition of hypoglycemia as a distinct clinical syndrome.

The discovery that a similar syndrome followed an overdose of insulin and the recent introduction of inducing hypoglycemia as a therapeutic procedure in psychiatric practice have led to the general recognition of the syndrome of hypoglycemia, so that the details need not be discussed here.

The literature dealing with hypoglycemia for the most part stresses the element of hyperinsulinism, whether therapeutic or spontaneous from association with tumors or hyperfunction of the islands of Langerhans. Clinical cases of hypoglycemia of hepatic origin are relatively rare but still occur with sufficient frequency that this possibility should not be overlooked. The pathologic lesions which may produce this syndrome are varied, and hypoglycemia is not characteristic of any specific hepatic lesion. The report of the first case, one of toxic hepatitis following the administration of neoarsphenamine, was made by Cross and Blackford⁵⁵. An extensive primary carcinoma of the liver was responsible for hypoglycemia in the cases reported by Nadler and Wolfer⁵⁶ and by Crawford⁵⁷. Josephs⁵⁸ and Judd, Kepler and Rynearson⁵⁹ described cases of hypoglycemia associated with fatty metamorphosis of the liver.

53 Mann, F. C. The Effects of Complete and of Partial Removal of the Liver, *Medicine* **6** 419 (Dec.) 1927.

54 Fischler, F. *Physiologie und Pathologie der Leber nach ihrem heutigen Stande*, ed. 2, Berlin, Julius Springer, 1925.

55 Cross, J. B., and Blackford, L. M. Fatal Hepatogenic Hypoglycemia Following Arsphenamine, *J. A. M. A.* **94** 1739 (May 31) 1930.

56 Nadler, W. H., and Wolfer, J. A. Hepatogenic Hypoglycemia Associated with Primary Liver Cell Carcinoma, *Arch. Int. Med.* **44** 700 (Nov.) 1929.

57 Crawford, W. H. Hypoglycemia with Coma in a Case of Primary Carcinoma of the Liver, *Am. J. M. Sc.* **181** 496 (April) 1931.

58 Josephs, H. Spontaneous Hypoglycemia in Childhood, *Am. J. Dis. Child* **38** 746 (Oct.) 1929.

59 Judd, E. S., Kepler, E. J., and Rynearson, E. H. Spontaneous Hypoglycemia. Two Cases with Fatty Metamorphosis of the Liver, *Am. J. Surg.* **24** 345 (May) 1934.

Howard⁶⁰ and Moore, O'Farrell and Headon⁶¹ have noted hypoglycemia in cases of acute yellow atrophy of the liver and of acute hepatitis, respectively. Sjöberg⁶² observed hypoglycemia in a case of fatal Weil's disease. More recently, Conn, Newburgh, Johnston and Sheldon,⁶³ Coller and Jackson⁶⁴ and Conn⁶⁵ have reported a series of 6 cases of hypoglycemia due to chronic cholecystitis with associated cholangitis and biliary cirrhosis. My associates and I have also had the opportunity of seeing 3 cases in which recognizable hypoglycemia occurred as part of the postoperative reaction following cholecystectomy. Rowntree⁶⁶ reported a similar case. It must, therefore, be concluded that hypoglycemia occurs as a result of hepatic insufficiency. When one considers the number of operations which are now performed on the biliary tract, it is fortunate that hypoglycemia is so rare a complication.

Hemorrhage—Hemorrhage is one of the commonest complications of hepatic disease. It accompanies severe hepatitis or acute yellow atrophy, and it has been the commonest cause of death following operation on patients with obstructive jaundice. The role of hypoprothrombinemia in causing this predisposition to hemorrhage and correction of the disorder by the therapeutic use of vitamin K have already been discussed.

The gastrointestinal hemorrhages that are so serious a complication of portal cirrhosis usually result from rupture of esophageal varices. Esophageal varices are one manifestation of the syndrome of portal hypertension which already has been discussed. The importance of the roentgenologic demonstration of esophageal varices has recently been emphasized by Schatzki.⁶⁷ The management of this condition has been discussed by Walters, Moersch and McKinnon.⁶⁸ Crafoord and

60 Howard, C. P. Incidence and Clinical Diagnosis of Acute Yellow Atrophy of the Liver, *Tr. A. Am. Physicians* **46** 141, 1927.

61 Moore, H., O'Farrell, W. R., and Headon, M. F. Spontaneous Hypoglycemia Associated with Hepatitis, *Brit. M. J.* **1** 225 (Feb. 10) 1934.

62 Sjöberg, S. G. Malignant Cases of Weil's Disease, with Especial Reference to Early Diagnosis, *Acta med. Scandinav.* **98** 536, 1939.

63 Conn, J. W., Newburgh, L. H., Johnston, M. W., and Sheldon, J. M. Study of the Deranged Carbohydrate Metabolism in Chronic Infectious Hepatitis, *Arch. Int. Med.* **62** 765 (Nov.) 1938.

64 Coller, F. A., and Jackson, H. C. Surgical Aspects of Hypoglycemia Associated with Damage to the Liver, *J. A. M. A.* **112** 128 (Jan. 14) 1939.

65 Conn, J. W. The Spontaneous Hypoglycemias: Importance of Etiology in Determining Treatment, *J. A. M. A.* **115** 1669 (Nov. 16) 1940.

66 Rowntree, L. G. Certain Clinical and Terminal Pictures in Hepatic Disease. *M. Clin. North America* **13** 1399 (May) 1930.

67 Schatzki, R. Roentgen Demonstration of Esophageal Varices: Its Clinical Importance, *Arch. Surg.* **41** 1084 (Nov.) 1940.

68 Walters, W., Moersch, H. J., and McKinnon, D. F. Bleeding Esophageal Varices: An Evaluation of Methods Directed Toward Their Control, Especially by Direct Injection of a Sclerosing Solution, *Arch. Surg.* **41** 1101 (Nov.) 1940.

Frenckner⁶⁹ reported successful injection of sclerosing solution into the varices through the esophagoscope. Now Moersch reports 6 cases in which the injection of a solution of sodium morrhuate into the varices through the esophagoscope has been successful in causing their obliteration. This is a brilliant technical achievement on the part of Moersch and gives promise of being of great therapeutic value.

HEPATORENAL SYNDROME

Renal insufficiency is one of the serious postoperative complications of obstructive jaundice. It has attracted a great deal of attention, particularly among surgeons, and has been emphasized under the title of hepatorenal syndrome. A large literature has resulted, which has been the subject of a review by Wilensky.⁷⁰

Patients with the hepatorenal syndrome show a clinical picture which is fairly characteristic. The manifestations develop slowly. In a few cases the symptoms are mild and consist of increasing mental lethargy, gastrointestinal disturbances and a diminished output of urine. There is a concomitant retention of urea and other nitrogenous substances in the blood. Under the influence of the forced administration of large amounts of fluid containing dextrose and sodium chloride, and occasionally transfusions, the picture improves, the urinary flow is reestablished, the laboratory findings return to normal and the patient recovers.

In cases of more severe form there is no improvement. The clinical symptoms increase in severity, the lethargic state is replaced by coma, the gastrointestinal symptoms increase and jaundice frequently appears or increases in intensity. The urinary output decreases, or there may be complete suppression of urine. Carphologia, subsultus tendinum and occasionally convulsions appear. Death follows shortly.

Postmortem examination shows changes in both the liver and the kidneys. There are shrinkage and cytoplasmic granulation of the hepatic cells about the central veins. The biliary canaliculae and the smaller bile capillaries are plugged with pigmented material. Various degrees of necrotic change are observed in the hepatic cells, especially those of the central portion of the lobule and about the larger bile ducts. The stellate cells of Kupffer are swollen and seem to show increased activity.

In the kidney, the convoluted tubules and the loops of Henle show extensive parenchymatous degeneration. In many tubules the nuclei are pale and hazy and apparently are undergoing lysis. Other tubules seem

69 Crafoord, C, and Frenckner, P. New Surgical Treatment of Varicose Veins of the Oesophagus, *Acta oto-laryng* **27** 422, 1939.

70 Wilensky, A. O. Occurrence, Distribution and Pathogenesis of So-Called Liver Death and/or the Hepatorenal Syndrome, *Arch Surg* **38** 625 (April) 1939.

to have undergone complete necrosis. The epithelium lining Bowman's capsule is swollen, as is the endothelium of the capillary loops. The collecting tubules contain granular albuminous precipitate and casts. The various attempts to explain these changes have in general been made from one or the other of two opposed points of view. On the one hand there is the view, championed by Helwig and Orr and their associates,⁷¹ Boyce and McFetridge⁷² and many others, that patients with this syndrome are "liver weaklings." It is assumed that they are able to endure the hepatic damage which they have suffered as long as they are subjected only to the stress and strain of ordinary life. They cannot, however, withstand the added ordeal of anesthesia, the trauma of surgical manipulation, the drop of intra-abdominal temperature, the changes in hepatic and biliary pressure and the other factors introduced by surgical procedures involving the liver or biliary tract.

When hepatic function fails, the toxic substances which reach the liver in the course of the normal metabolic processes are no longer detoxified. The kidney then attempts to take over the function of detoxification. It must deal not only with toxic substances which the liver is unable to handle but with specific toxic substances formed from necrosing hepatic cells. The margin of reserve in the kidney is slight. It promptly breaks down in its turn, and an overwhelming and lethal toxemia is the natural consequence. Boyce^{72b} reports that he has no doubt that hepatic damage always precedes renal damage and that prompt death with hyperpyrexia, manifestations and deferred death with uremic manifestations are phases of the same pathologic process.

The tendency has been to widen the use of the term hepatorenal syndrome. At first it was limited to conditions developing in the biliary tract after operation, with or without jaundice, or accompanying cholelithiasis or cholangitis. Cases of traumatic injury to the liver were also included. Wilensky lists a great variety of conditions in association with which the hepatorenal syndrome has been described. In many of the cases the syndrome is reported as following abdominal and other operations in which the liver and biliary tract were not primarily involved. Included in his compilation are carcinoma of the breast, gastric ulcer, poisoning by cinchophen or allied compounds, poisoning

71 Schutz, C. B., Helwig, F. C., and Kuhn, H. P. A Contribution to the Study of the So-Called Liver Death, *J. A. M. A.* **99** 633 (Aug. 20) 1932. Orr, T. G., and Helwig, F. C. Liver Trauma and Hepatorenal Syndrome, *Ann. Surg.* **110** 682 (Oct.) 1939.

72 (a) Boyce, F. F., and McFetridge, E. M. "Liver Deaths" in Surgery: Analysis of Thirty-Four Cases, with New Explanation of Clinical and Pathological Picture, *New Orleans M. & S. J.* **88** 563 (March) 1936. (b) Boyce, F. F. Hepatic and Biliary Tract Disease. A Review of Recent Significant Advances, *Ann. Surg.* **109** 351 (March) 1939.

by a great variety of drugs and chemicals, especially by phosphorus, chloroform, asphenamine and diethylene glycol, toxemia of pregnancy, the thyroid crisis of acute thyrotoxicosis, burns, intestinal obstructions, alkalosis, infections and bacteremia, leptospirosis, or Weil's disease, acute yellow atrophy, or icterus gravis, hyperpyrexia from artificial fever, anesthesia, shock, tissue necrosis, and biliary peritonitis.

Opponents of the view that the hepatorenal syndrome is the result of a specific toxic process argue that the variety of conditions just listed is evidence either of the effect of a great number of toxic agents or of a faulty use of the term.

Wilensky points out that the association of hepatic and renal damage in pathologic conditions is frequent because the two organs are the chief means of excretion after metabolic change has taken place. My experience has been in complete accord with this point of view.

The liver is the chief agent for the neutralization of poisonous substances absorbed from the alimentary tract, whether introduced as such or formed during the process of digestion. The kidney is the chief means of elimination of toxic substances which the body is unable to neutralize. When excretion by the liver becomes impossible, whether from blocking of the bile ducts or from parenchymal destruction, the kidney takes on the eliminatory function of the liver. It would seem that with the conditions previously listed, the two essential features of the hepatorenal syndrome, hepatic lesions and renal lesions, do not always occur and that they do not occur with equal intensity. It is generally accepted that a great variety of agents is capable of producing hepatic injury. The variety of substances which may produce renal damage is equally diverse. Experimental studies have shown that a considerable number of chemical compounds, such as chloroform, phosphorus, carbon tetrachloride or diethylene glycol, have an injurious effect on both the liver and the kidneys. The relative intensity of the changes produced depends on the method of administration, the dosage, the previous diet of the animal, differences in individual susceptibility and a variety of other factors.

Experimental attempts to produce the hepatorenal syndrome in animals have been only partially successful and have failed to demonstrate the role of a characteristic and specific toxin in the pathogenesis of this condition. It is clear, therefore, that the hepatorenal syndrome develops in consequence of the action of more than one precipitating factor.

Whatever the poisons are, they affect both the liver and the kidneys. They may be exogenous in origin, or they may develop within the body. They may be chemical drugs and poisons, toxins resulting from bacterial growth or products of destruction of the various tissues of the body. They may be formed during metabolism or arise in the intestinal canal during digestion.

Once this chain of anatomic and functional disturbances is initiated other factors, such as fever, shock, autolysis of tissue anoxemia anhydremia and azotemia, come into play. These aid and abet the primary agents by creating conditions which are capable of producing further cellular degeneration in the parenchymatous organs. A vicious cycle, therefore, is produced and the primary injury greatly accentuated. The development of the hepatorenal syndrome is of serious prognostic importance in both medical and surgical cases and therefore should be recognized at the earliest possible moment. It is due to the action of a variety of possible agents, so that further study of the pathogenesis of the condition is desirable.

ICTERUS GRAVIS, OR ACUTE YELLOW ATROPHY OF THE LIVER

According to Legg⁷³ Morgagni is generally credited with the first report of an authentic case of acute atrophy of the liver, though a possible case was reported by Ballonius. Since then numerous cases have been reported. Bright was one of the first English physicians to record this disease, and his report was followed by others, notably that of Budd. It was the work of the Viennese school, especially that of Horacek, Rokitsky and Frerichs, that firmly established this disease as a clinical and pathologic entity. More recent descriptions have been given by Legg,⁷³ Miller and Rutherford,⁷⁴ Howard⁶⁰ and others.⁷⁵

The disease usually begins as a gastrointestinal upset with nausea, anorexia, epigastric distress and generalized malaise. These prodromal symptoms frequently are so slight as to be overlooked entirely.

The appearance of bile in the urine often precedes the development of jaundice. The clinical signs of jaundice vary considerably in degree, and at this stage the condition is not to be differentiated from the ordinary benign type of acute jaundice.

The increasing severity of the symptoms and rapid progress of the disease are the most characteristic manifestation of acute yellow atrophy. The commonest nervous manifestation is drowsiness. This, however, may be preceded by a period of extreme excitement beginning with headache, restlessness, mental confusion and delirium and may be

73 Legg, J. W. *On the Bile, Jaundice and Bilious Diseases*, New York: Appleton & Co., 1880.

74 Miller, J., and Rutherford, A. *Liver Atrophy*. *Quart J Med* **17**: 81 (Oct.) 1923.

75 Phillips, J., and Haden, R. L. *The Diagnosis and Treatment of Diseases of the Liver and Biliary Tract*, in Christian, H. A. *Oxford Monographs on Diagnosis and Treatment*, New York: Oxford University Press, 1936, vol. 8. Miller, T. G., and Machella, T. E. *Diseases of the Liver*, in Nelson *New Loose-Leaf Medicine*, New York: Thomas Nelson & Sons, 1940, vol. 5, p. 471. Elliot, C. A., and Nadler, W. H. *Diseases of the Liver*, in Tice, F. *Practice of Medicine*. Hagerstown, Md., W. F. Prior Company, Inc., 1940, vol. 7, pp. 59-137.

accompanied by muscular twitching or generalized convulsions. After the access of the delirium the patients fall again into a drowsy state, and by degrees this passes over into a profound coma.

In some cases there is a hemorrhagic diathesis, which may appear in the form of a purpuric eruption or as a persistent oozing from the mucous surfaces and the gastrointestinal canal. The pulse, respiration and temperature frequently are unchanged during the early period of the disease, later the pulse rate increases considerably. When the patient becomes comatose, the respiration becomes slow and stertorous, and a marked premonitory rise in temperature has been described. At necropsy reduction in the size of the liver and slight enlargement of the spleen usually are present. Changes in these two organs are important when they can be demonstrated clinically, but this is often difficult, if not impossible. Nausea and vomiting and tenderness in the epigastrium and along the right costal margin are frequent accompaniments of this disease. Ascites is seen occasionally.

Hepatic Coma.—Progressively increasing weakness and loss of appetite frequently are accompaniments of chronic disease of the liver. An increase in the severity of these symptoms associated with nausea often is of evil omen. The patient then becomes drowsy, and this drowsiness progressively deepens until it imperceptibly passes into stupor and coma. The respiration is unchanged at first but later may be irregular and of either the Cheyne-Stokes or the Biot type. In profound coma the respiration is usually slow and stertorous. The pulse rate and temperature usually show no change, but either may be markedly elevated. Nervous symptoms usually comprise a mild excitation with delirium at the onset, while the patient later passes into a typhoidal state. Rarely are there muscular twitchings and convulsions. In my experience, however, the symptoms of excitation are slight and the progressive lethargy with the development of drowsiness and coma dominates the clinical picture.

This terminal picture is similar to that seen in cases of acute yellow atrophy of the liver. It is not characteristic of the latter disease alone, for it is seen in other conditions in which there has been extensive hepatic damage. I have seen this clinical picture develop in the terminal stages of acute yellow atrophy of the liver, in fatal Weil's disease, in toxic jaundice caused by administration of arsphenamine or poisoning by carbon tetrachloride, in toxic hepatitis resulting from eclampsia, in both portal and obstructive cirrhosis and in extensive carcinomatous destruction of the liver, whether primary or secondary, and as a sequela of operations on the gallbladder or the biliary tract. This syndrome has developed independently of the presence or absence of such symptoms as jaundice or ascites and is not related to the degree of biliary obstruction.

The pathogenesis of this condition is still undetermined. Leyden⁷⁶ expressed the belief that the toxic symptoms resulted from retention of and poisoning by bile acids. By analogy to uremia, he named the syndrome cholemia, and this term has persisted, though the evidence is all against such a theory. Flint⁷⁷ expressed the opinion that cholesterol was the toxic agent and named the disorder cholesteremia. Because of the apparently severe toxemia or intoxication it has been called hepatic intoxication. Other writers have stressed the evidence of hepatic insufficiency. This point of view led Frerichs⁷⁸ to use the term acholia and Quincke and Hoppe-Seyler⁷⁹ to suggest hepatargia, from ἀργία, or inactivity.

My own studies have failed to show any significant change in the chemical composition of the blood occurring with such consistency that it could be considered as characteristic. In individual cases extreme changes in the chemical composition of the blood may occur, but these changes are significant only with regard to the individual case and not to the group as a whole. Intoxication due to the retention of any of the three chief constituents of the bile is to be excluded. The determination of the bile acids in the blood shows no consistent increase. The clinical picture is not related to the level of either cholesterol or bilirubin in the blood serum. The amino acids in the blood are increased in cases of acute yellow atrophy when there is rapid destruction of the liver but not in cases of less acute disease. The blood urea is elevated when there is associated renal insufficiency. The infrequency of hypoglycemia has been mentioned. Hypoprotinemia apparently is responsible for the hemorrhagic tendency seen in cases of this disease, but this symptom is not present in all instances. Changes in the guanidine, lactic acid or uric acid of the blood are not constant. Neither acidosis nor alkalosis is characteristic. The same may be said regarding the other chemical constituents of the blood that I have studied. In view of the pronounced evidence of hepatic injury seen in cases of this condition and the absence of direct evidence of a proved toxic agent, one is forced to the view that the syndrome is to be related to hepatic insufficiency.

The experimental picture of hepatic insufficiency produced by extirpation of the liver is dominated by the resultant hypoglycemia. The latter can be controlled by the injection of dextrose. Under these conditions

76 Leyden, E. *Beiträge zur Pathologie des Icterus*, Berlin, A. Hirschwald, 1866.

77 Flint, A., Jr. *Experimental Researches into a New Excretory Function of the Liver*, *Am. J. M. Sc.* **44**: 305, 1862.

78 Frerichs, F. T. *A Clinical Treatise on Disease of the Liver*, London, New Sydenham Society, 1860.

79 Quincke, H., and Hoppe-Seyler, G. *Die Krankheiten der Leber*, Vienna, Alfred Holder, 1899.

Mann⁵³ has reported the development of a different terminal picture in the dog. It becomes restless and usually vomits. It breathes with considerable difficulty, though dyspnea and an hunger do not seem to be the cause. The animal becomes ataxic, and the senses of sight and hearing apparently are diminished or lost. Coma, which may persist for several hours, develops. Death usually is sudden and quiet.

The drawing of an analogy between clinical findings in patients and experimental observations in animals is a prolific source of error unless precise objective changes can be used to confirm subjective impressions. That is true in the present case, and there is no direct proof that the clinical and experimental syndromes are related. Nevertheless, it is probable that they are intimately associated and an explanation of the factors producing death of the hepatectomized dog would go far in explaining the clinical picture of hepatic insufficiency.

One need not seek for a single specific hepatic toxin. An analogy may be drawn to the uremic syndrome, which is quite as distinct clinically as is the syndrome of hepatic coma. The pathogenesis of uremia is not entirely clear, but recent investigators, such as Fishberg⁸⁰ and Harrison and Mason⁸¹ insist that they have been unable to establish the retention of any single substance which will produce the clinical syndrome of uremia. They report rather that uremia is a complex autointoxication which is the summation of the effects of retention of various urinary constituents.

Mann⁸² has stressed the multiplicity of the functions of the liver and its essential nature as the chief storehouse and chemical factory of the body. This is an essential role, and his description of the liver as the commissariat of the body is apt. Any interference with these manifold activities of the liver is difficult because of the large reserve of this organ, but once this reserve is exhausted and true hepatic insufficiency produced, serious disturbances in the intermediary metabolism and *milieu interieur* of the body are unavoidable. Not only the results of failure of the liver but also the effects of secondary disturbances in other organs may logically be expected. It is probable, therefore, that the clinical picture of hepatic insufficiency or hepatic coma is to be explained not as the effect of a yet undiscovered toxin or poison but rather as the summation of the effects of the failure of its manifold activities and the inability of the organism to maintain life after the failure of so vital an organ.

80 Fishberg, A. M. Hypertension and Nephritis, ed. 3, Philadelphia, Lea & Febiger, 1934.

81 Harrison, T. R., and Mason, M. F. The Pathogenesis of the Uremic Syndrome, *Medicine* **16**: 1 (Feb.) 1937.

82 Mann, F. C. The Role of the Liver as the Commissariat of the Body, *Am. J. Digest. Dis. & Nutrition* **4**: 355 (Aug.) 1937.

Book Reviews

Clinical Diabetes Mellitus and Hyperinsulinism By Russell M Wilder, M D, Ph D, F A C P, Professor and Chief of the Department of Medicine, the Mayo Foundation for Medical Education and Research, University of Minnesota, and Head of the Section on Metabolism Therapy, Division of Medicine, the Mayo Clinic, Rochester, Minn Cloth Price, \$6 Pp 459 Philadelphia W B Saunders Company, 1940

Here is the long-awaited presentation in monograph form of Dr Wilder's past experiences and present day views in the field of diseases of carbohydrate metabolism. Although he limits his thesis to a consideration of procedures useful in the diagnosis and treatment of diabetes mellitus and hyperinsulinism, he keeps his subject matter alive and stimulating by the use of argumentative footnotes. The material is well organized and written in a plain, readable style.

The initial chapter, on the normal homeostasis of the blood sugar and the various regulatory mechanisms involved in normal carbohydrate metabolism, serves admirably to introduce Dr Wilder's definition and diagnostic standards of diabetes mellitus in its varied clinical forms. He adheres strictly to the unitarian concept of diabetes mellitus as a disease characterized by a persistently abnormal metabolism due to a real or relative insufficiency of the insulinogenic ability of the pancreas. In the discussion on the varied clinical types of diabetes some criticism might be offered against what seems an unusual emphasis on the type of dextrose tolerance curve, since it is not uncommon to find such tolerance curves varying widely in individual patients, either with diabetes or without it.

Dr Wilder recognizes as the basic cause of diabetes an insufficiency of insular reserve (bioplasmic inferiority, probably hereditary). Provocative causes are grouped in two categories. The first includes diseases which directly depress the function of the islet cells, such as acute or chronic pancreatitis, pancreatic stones or cysts, secondary degenerative lesions and hemochromatosis, and the second, such disturbances as obesity, endocrinopathies, organic or functional diseases of the nervous system and climatic changes. One may wonder at the more than usual emphasis on the climate as a provocative agent and the scanty discussion of a deficient blood supply to the pancreas as a factor in causing islet cell depression. Dr Wilder's suggestions as to the prevention of diabetes mellitus are stimulating, but the ideas of mass migration of persons with diabetes and their siblings to more temperate climates and the limiting of diabetic families to one or two children will not go unchallenged in many quarters.

The chapters on the treatment of diabetes are excellent and should serve as a dependable guide. Certain of the requirements for effective therapy will be difficult for the average physician to fulfil, but nevertheless are necessary and optimal for the proper care of the diabetic patient. It is hoped that Dr Wilder's attitude toward the use of insulin will help dispel the fears of it held by many persons with diabetes and not a few of their physicians. The sections on diet therapy, diet substitutions and cookery give a practical foundation of the principles of dietetics. There is an apparent middle-of-the-road policy in regard to the high fat-low carbohydrate versus low fat-high carbohydrate argument, although the diet lists in the appendix would indicate no reticence in the use of diets fairly high in fat. The carbohydrate allowance is neither high nor low, and undernutrition is not recommended. Useful tables of food values, normal weights and heights and the excellent food nomogram used at the Mayo clinic are included for the convenience of the physician.

Ample space is given to the discussion of the complications of diabetes mellitus and their treatment. The rationale back of the therapeutic measures

advocated in the treatment of diabetic acidosis is explained, and the routine management is, for the most part, commendable. Exceptions may be taken to the validity of Dr Wilder's reasons for prescribing digitalis and the intravenous administration of sodium bicarbonate. Advocating cesarean section for the delivery of all diabetic mothers and the sterilization of the mothers seems illogical and dangerous in the present state of knowledge. The chapter on diseases of the thyroid gland is excellent. Surgical removal of all thyroid adenomas whether or not associated with hyperthyroidism would seem justified by the results obtained and on physiologic grounds.

The chapters on hyperinsulinism are extremely valuable because of Dr Wilder's original contributions to this subject. The definition and diagnostic interpretations will be valuable in helping to sort out instances of hyperinsulinism from among the many diseases causing hypoglycemia, which, Dr Wilder indicates, are not often due to true islet cell adenomas. Included is a detailed review of 12 cases. It is hoped that the inclusion of hyperinsulinism in a monograph on such a common disease as diabetes will further the search for more instances of this interesting condition.

The wide experience of Dr Wilder makes this book an extremely valuable one for general use and for teaching purposes. It should be required reading in medical schools because it presents a practical consideration of a common disease in a readable style and because it illustrates how well an authority can present his views on a subject and still encourage sound criticism and investigation. The bibliographic material is well chosen and admirably grouped at the end of each chapter.

The Head and Neck in Roentgen Diagnosis By Henry K. Pancoast, M.D., Eugene P. Pendergrass, M.D., and J. Parsons Schaeffer, M.D., Ph.D. Price, \$12.50. Pp. 902, with 1,251 plates. Springfield, Ill. Charles C. Thomas, Publisher, 1940.

In 902 pages of text with a complete bibliography, the authors have written a book which should be of extreme interest not only to the roentgenologist but to the orthopedist, the otolaryngologist, the neurologist and the surgeon. It is one of few books written on this subject and, therefore, a great contribution to medical literature.

The first chapter covers the anatomy of the skull as well as anatomic variations and anomalies. The second chapter should appeal to surgeons, especially those treating head injuries. The subject is covered in detail from a diagnostic standpoint. The technical factors and procedures necessary for good roentgenograms are ably presented and illustrated throughout the book.

In the preface, the authors have stated that modern medical roentgenology cannot merely be concerned with the purely technical aspects of the subject, but must variously be correlated and integrated with certain aspects of fundamental and variational morphology, function, pathology and clinical observation. While the finished volume should, therefore, occupy an important niche in the library of every roentgenologist, it should also prove invaluable as a reference work for specialists interested in the head and neck. The book should be commended for the able presentation of many unusual conditions, so often omitted from the ordinary textbook.

There is an excellent chapter on all intraorbital and intra-auricular foreign bodies, which should be of interest to the ophthalmologist and otologist, as well as the roentgenologist. Virtually one fourth of the book deals with intracranial tumors and the technic and diagnosis in cerebral pneumography. A general consideration of tumors of the brain and also their classification are dealt with in an instructive and concise manner. The chapter on cerebral pneumography describes the indications and contraindications and the technic used by the authors. The roentgenologic interpretation of intracranial tumors is well explained.

and illustrated. The part of the discussion dealing with the differentiation of the normal and the pathologic and the need of being familiar with the normal is of extreme importance.

In the last 129 pages the anatomy and pathology of the neck are considered thoroughly, even beyond the expectations of the trained roentgenologist. The demonstrations of the soft tissues of the neck are well illustrated in the roentgenographic reproductions. Usually a drawing, photograph or diagram of a cross section is used for comparison and identification of the structures. The anatomic and roentgenologic illustrations are of excellent quality throughout the book, and the numerous captions placed opposite each illustration are a great aid to the reader.

The authors are to be congratulated on the compilation of this book. They have demonstrated great experience and an unlimited fund of information.

The Electrocardiogram in Congenital Cardiac Disease. A Study of 109 Cases, 106 with Autopsy. By Maurice A. Schnitker, M.D. Cloth. Price \$3. Pp. 147, with illustrations. Cambridge, Mass. Harvard University Press, 1940.

The author reports the electrocardiographic observations on 109 patients with congenital heart disease. In 106 instances material from autopsy was available, and in 1 other instance the diagnosis was corroborated by surgical intervention. The patients are discussed under three general headings: the acyanotic group, the late cyanotic group and the cyanotic group. Within each group individual lesions or combinations of lesions are considered.

In most cases there was no specificity of the electrocardiographic changes in a given type of congenital cardiac disease. Specific changes occurred only in congenital heart block, in dextrocardia and in disease of the tricuspid valve. In most instances the electrocardiogram gave no clue which would differentiate congenital from acquired heart disease.

Of the 106 patients, right axis deviation was present in 36 per cent, left axis deviation in 21 per cent and no preponderance in 43 per cent.

Large, biphasic QRS complexes were found in one or more leads in 30 per cent of the patients and were most frequently associated with defects of either the auricular or the ventricular septum. Disturbances of conduction varying from a prolonged PR interval to complete heart block were also found frequently in cases of defect of either septum. High and pointed P waves or auricular fibrillation occurred chiefly with defect of the auricular septum.

A point of interest stressed by the author was the frequent presence of acquired rheumatic heart disease in conjunction with the congenital cardiac disease. Post-mortem examination revealed that 28, or 26 per cent, of the 106 patients had evidence of rheumatic valvular disease.

The author has made a valuable contribution which should prove of interest to every student of congenital heart disease.

The Merck Index. An Encyclopedia for the Chemist, Pharmacist, Physician, Dentist and Veterinarian. Fifth edition. Price, \$3. Pp. 1,060. Rahway, N. J. Merck & Co., Inc., 1940.

The Merck Index has appeared in repeated editions since 1889 and hardly needs any introduction to the medical profession. It is a one volume encyclopedia constituting an extensive and almost complete reference work for various drugs and chemical compounds used in the medical sciences.

The new edition is similar in format to the previous editions, but enlarged to include all of the new drugs and chemicals which have come into use since the last edition, in 1930. To the complete information on the various chemical compounds and drugs and their formulas, dosage and usage, which appeared in the previous editions, much valuable material has been added, including a section on the coal tar dyes whose use is permitted in foods, drugs and cosmetics, a table of indicators used for acid-base titration and pH determination, a complete section

devoted to the chemical and clinical-chemical reactions, tests and reagents, classified under each author's name, with references to the literature in each case, a section on culture mediums, fixatives and staining solutions, and a section on antidotes for poisons

This volume is of direct value to physicians, druggists and laboratory workers as a guide and ready reference. The medical profession owes a debt of gratitude to Merck & Company for this complete and almost indispensable reference work.

Clinical Heart Disease Second edition. By Samuel A. Levine, M.D., Assistant Professor of Medicine, Harvard Medical School. Price, \$6. Pp. xiv, plus 495, with 109 illustrations. Philadelphia: W. B. Saunders Company, 1940.

The first edition of this book appeared in 1936. It was flatteringly reviewed in the *ARCHIVES* (59:1112-1113 [June] 1937). The reviewer said that the author of a textbook of medicine should be able to write clearly and concisely, should have something to teach and considerable experience in teaching it, should have a comprehensive experience covering the field about which he writes and, finally, should not hesitate to state ideas which have stood critical, practical tests in his own experience. Dr. Levine seemed to have met this formula happily, and the first edition of his book was deservedly popular.

Now the second edition appears. It is much like the first in form and contents except for a new chapter on medicolegal aspects of heart disease. Luckily, an unfortunate typographic error in regard to the dose of cyanide for circulation time was detected and corrected before any harm could be done.

Dr. Levine is wise. First he designed a good model for a useful book. Now he has perfected this model, taking from it what various critics have regarded as of inferior quality and adding to it new touches here and there so as to bring the contents up to date. The result is a better book than the first, more informative, with finer polish and greater readability. It continues to be what it was originally planned for, a book of great value to the general practitioner as well as to the physician who attempts to qualify as a specialist in the treatment of cardiac disease.

Fundamentals of Nutrition By Estelle E. Hawley, Ph.D., and Esther E. Mauer, M.D. Price \$5, postpaid. Pp. 385. Springfield, Ill.: Charles C. Thomas, Publisher, 1940.

If good nutrition is our first line of defense, then this book should help in building that line, for it is full of sane and sound advice on nutrition. If you are underweight it tells you how to gain, if overweight how to reduce, if allergic (and who is not?) how to plan your menu. If your income is not what it should be there are low cost meals, and if you have not been taking your daily allotment of vitamins there are pictures so revealing that you will immediately run to the corner drugstore or the kitchen cupboard before you, too, become "even as one of these."

The table of 100 calory portions is unique in that it includes the relative cost of each food and an outline for planning of menus. Another feature is a special diet form for use in cases of obesity, ulcers, diabetes, hypoglycemia and other disorders.

This book is so full of information on nutrition, diet and menu planning that it should prove most helpful to any one wishing up-to-the-minute information on foods.

Convalescent Care Proceedings of the Conference Held Under the Auspices of the Committee on Public Health Relations of the New York Academy of Medicine, Nov. 9 and 10, 1939. Pp. 261. New York: New York Academy of Medicine, 1940.

In this volume are presented the discussions on convalescent care occurring at the conference held for that purpose in New York. Convalescent care for the various types of medical or surgical patients or those with neurologic diseases is discussed in detail with reference to the medical, social and economic aspects.

The necessity for proper convalescent care after even minor illnesses, and certainly after severe infections, has at no time received the attention which it should from the attending physician. Surgical patients have been largely neglected. Patients with cardiac disease have received some attention, but only in certain cities, and even this has been inadequate. Not only is convalescent care necessary for the welfare of these patients as regards restoration to a normal level of health and usefulness, but it is important as one means of reducing the cost of medical care to the patient and to the community.

This volume is recommended to all physicians, regardless of the type of practice. It is hoped that the conference and this volume will breathe new life into a phase of medical care which, as Dr. Corwin says in his address, "has remained almost completely static, isolated and anemic."

Chemistry and Medicine Papers Presented at the Fiftieth Anniversary of the Founding of the Medical School at the University of Minnesota. Edited by Morris B. Visscher. Price, \$4.50. Pp. 293, with charts and illustrations. Minneapolis: University of Minnesota Press, 1940.

This volume comprises the papers presented in a program, given in October 1939, which was planned to commemorate the semicentennial anniversary of the founding of the medical school at the University of Minnesota. The papers read on this occasion were chosen to center on one theme, "Some Trends in Medical Progress, with Particular Reference to Chemistry in Medicine," and were presented by men especially qualified to discuss each particular trend. Several guest speakers from other universities were included. It is not within the scope of this review to present comment on the individual papers. The subjects are set forth under four main headings: "Progress in the Application of Physical Chemistry to Medicine," "Some Recent Investigation in Metabolism," "Some Aspects of Immunity and Chemotherapy," and "Some Approaches to the Nervous Control of the Organism." The papers presented were each of interest and importance to the student of medicine and were of uniform excellence. They constitute a lasting memorial to the establishment of a great institution of teaching which has made so many valuable contributions to medical science.

Lehrbuch der Bäder und Klimaheilkunde By German Authors. Edited by Prof. Dr. H. Vogt. Vols. 1 and 2. Price, 93 marks. Pp. 1,227. Berlin: Julius Springer, 1940.

These two volumes of many pages and great weight (25 Kg.) represent the yearly compilation of contributions on hydrotherapy, physical therapy and climatic therapy by German physicians. They are written with the usual German punctilious attention to details. Some of the sections may appeal to American physicians, such as the article presented by Bacmeister on the climatic treatment of tuberculosis. For the most part, the subject matter will have but little interest for practitioners of medicine, most of whom are not interested, for instance, in analyses of mineral waters or the special chemistry of mineral springs. The ordinary practitioner of medicine is somewhat skeptical concerning the value of bitter waters in relieving conditions of the stomach, intestine or gallbladder, and probably is even less interested in knowing about the special springs, spas, watering places and bathing establishments in Germany.

The Compleat Pediatrician By W. D. Davison. Third edition. Price, \$3.75. Pp. 267. Durham, N. C.: Duke University Press, 1940.

When the reviewer discussed the second edition of this book, he pointed out that the synopsis method, possibly bad in principle, was vindicated in this instance by the skill and knowledge of the author. The same point of view applies to the present (third) edition. Everything in pediatrics seems included, and when the reader has learned to find his way about the book, as the author suggests, should be a real *vide mecum*.

News and Comment

Scientific Session of the American Academy of Physical Medicine —

The nineteenth annual meeting and scientific session of the American Academy of Physical Medicine will be held on April 28, 29 and 30, 1941 in New York. Lectures, symposiums, clinical papers, motion pictures and exhibits will be presented at the Hotel Pennsylvania. Clinics will be held at the Medical Center, New York Orthopedic Hospital, New York Post-Graduate Hospital and the Skin and Cancer Hospital. There will be an evening session at the Academy of Medicine Building and a banquet at the Hotel Pennsylvania.

Physical medicine in relation to general medicine and the specialties will be the underlying theme of the discussions, which will be based on new developments in electrotherapy, electrosurgery, radiation therapy, hydrology, physical education, military medicine and aviation medicine and on laboratory reports on related investigation.

All members of the medical profession and those of related interests are invited to attend the scientific program. There will be no registration fee.

Inquiries may be sent to the secretary, Dr. Herman A. Osgood, 144 Commonwealth Avenue, Boston.

American Heart Association—The seventeenth scientific meeting of the American Heart Association will be held May 30 and 31, 1941, at the Hotel Statler, Cleveland.

PRESSOR PROPERTIES OF EXTRACTS FROM NORMAL AND FROM ISCHEMIC KIDNEYS

J R WILLIAMS JR, M D

NASHVILLE, TENN

ARTHUR GROLLMAN, M D

BALTIMORE

AND

T R HARRISON, M D

NASHVILLE, TENN

The problem of the possible significance of renin in the production of hypertension is fundamentally important in determining possible approaches to the therapeutics of this disorder. The available evidence on this point is, however, conflicting. Thus, Harrison, Blalock, Mason and Williams¹ and Prinzmetal, Friedman and Abramson² observed that extracts of ischemic dog kidneys cause a greater rise in blood pressure than do those of normal kidneys. On the other hand, Pickering and Prinzmetal³ failed to observe an augmented pressor effect in extracts of ischemic rabbit kidneys, while Beckwith and Chanutin⁴ found that the pressor activity of the kidney remnants of rats with hypertension due to subtotal nephrectomy was less than that of normal kidneys from rats with normal blood pressure.

This work was aided by grants from the Josiah Macy Jr Foundation and from Mr Joe Werthan.

From the Department of Medicine, Vanderbilt University School of Medicine, and the Department of Pharmacology and Experimental Therapeutics, the Johns Hopkins University.

1 Harrison, T R, Blalock, A, Mason, M, and Williams, J R, Jr. Relation of Kidneys to Blood Pressure. Effects of Extracts of Kidneys of Normal Dogs and of Dogs with Renal Hypertension on Blood Pressure of Rats, *Arch Int Med* **60** 1058 (Dec) 1937.

2 Prinzmetal, M, Friedman, B, and Abramson, D I. Nature of Arterial Hypertension with Special Reference to the Role of the Kidney, *Ann Int Med* **12** 1604, 1939.

3 Pickering, G W, and Prinzmetal, M. Some Observations on Renin, Pressor Substance Contained in Normal Kidney, Together with Method for Its Biological Assay, *Clin Sc* **3** 211, 1938.

4 Beckwith, J R, and Chanutin, A. The Pressor Effect of Kidney Extracts of Intact and Partially Nephrectomized Rats, *Am J Physiol* **128** 562, 1940.

Several possible explanations for the divergent results obtained by previous workers suggest themselves (1) differences in methods of preparation, (2) species differences of the animals (dog, rabbit, rat) from which the kidneys were derived, and (3) variations in the methods used in testing the extracts. The purpose of the present experiments was to test these several possibilities in an attempt to elucidate the contradictory results of previous investigators.

METHODS

Unilateral renal ischemia was produced in dogs by means of a Goldblatt clamp and in rats by partial obstruction of one renal artery with a silk ligature. After two to five days, extracts were prepared either by simple maceration of the kidneys with 2 volumes of 0.85 per cent solution of sodium chloride (saline extracts) or by grinding the kidneys into 10 volumes of 95 per cent ethyl alcohol, filtering, washing the alcohol-insoluble fraction with ether and extracting the final dried powder with a solution of sodium chloride (renin). In order to have sufficient material for repeated injections, the kidneys of 3 to 5 rats with unilateral renal ischemia were combined for each experiment.

As test objects for the pressor properties of these extracts normal rats anesthetized with pentobarbital sodium were used. The lower abdominal aorta was cannulated and connected to a small bore mercury manometer, heparin was used to prevent clotting. The extract was administered in doses calculated according to the formula

$$\frac{(\text{Body weight in grams})^{2/3} \times 2}{100} = \text{cubic centimeters to be administered}^5$$

In a few of the earlier experiments the same rat was employed for alternate injections of the extracts from the normal and the ischemic kidneys. However, in most of the observations each fraction was injected into several rats and the average rise in blood pressure computed, each animal being used for only a single injection.

RESULTS

In 4 of a total of 5 comparisons, the saline extract from the ischemic kidney of a dog gave a definitely greater pressor effect than that from the normal kidney, the reverse effect was observed in the remaining instance. Likewise, the renin solution prepared by precipitation with alcohol from the macerated ischemic kidney gave a greater pressor effect than the similarly prepared extract of the normal kidney in 4 of the 5 comparisons, no difference was noted in the fifth observation. The divergent results of previous workers cannot, therefore, be accounted for by variations in the technic of preparation of the extracts.

On repeating the experiments previously outlined with rats' kidneys, we obtained results contrary to those just described. In 4 instances the extract from the normal kidney had a greater pressor effect than that from the ischemic organ. In the fifth experiment there was no appreciable difference between the two.

In 3 instances the saline extract of the rat kidneys, after being tested, was put into the ice box and further injections were made on the following day. In 2 of these 3 instances the extract of ischemic kidney, which had exerted less pressor effect when injected immediately after extraction, displayed a greater pressor effect

⁵ Grossman, E. B., and Williams, J. R., Jr. Relation of Age to the Renal Pressor Substance, *Arch Int Med* 62:799 (Nov) 1938.

after standing for twenty-four hours in a refrigerator. Four other observations were made in which the extracts from both the normal and the ischemic kidneys were tested by injection immediately after they were prepared and after standing for various intervals. These experiments, which are illustrated in figure 1, showed clearly that the extracts of normal kidney tend on standing to lose their pressor activity, while the similarly prepared extracts of the ischemic kidney maintain their pressor effects, or even become more active with time. However, because of the limited number of injections which could be made from the extracts of the rats' kidneys, a larger series of experiments was carried out, in which various fractions prepared from the kidneys of dogs were used.

Changes in the Pressor Property of Extracts of the Normal and Ischemic Kidneys of Dogs—In the experiment illustrated in figure 2 A, saline extracts were prepared from the kidneys of a dog with unilateral renal ischemia of four days'

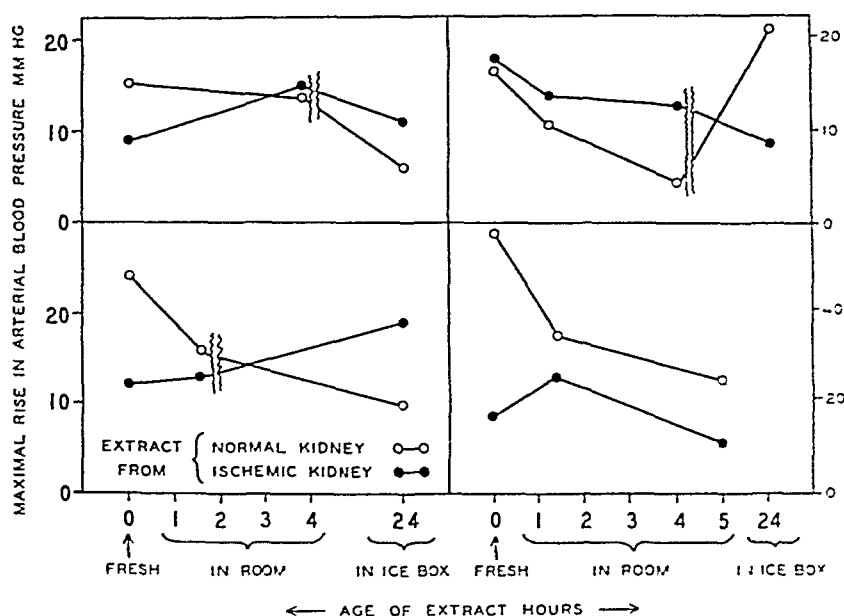


Fig 1—Saline extracts of the normal and the ischemic kidneys of the same rats were injected into other rats. Only the maximal pressor responses are recorded (each point represents the average maximal pressor effect in 2 rats). Although extracts from both normal and ischemic kidneys sometimes become more active and at other times less active, the general tendency was for the extracts of the normal kidney to lose pressor effect, while the extracts of the ischemic kidney tended to remain unchanged or even to become more active.

duration as rapidly as possible after their removal from the animal, under anesthesia induced with pentobarbital sodium. The extracts from each kidney were then immediately injected into each of 2 rats. The saline extracts were allowed to stand in a room at a temperature of 25 C and the injections repeated on 4 additional rats after one hour and seven hours. The pressor effect of the extracts from the ischemic kidney was initially about twice that of extracts from the normal kidney. On standing, the extract from the ischemic kidney gradually became slightly more pressor. The saline extract of the normal kidney, on the other hand, had lost practically all of its pressor effect at the end of one hour but had considerably more pressor effect than originally at the end of seven hours.

In 2 experiments in which the pressor principle from the normal and the ischemic kidney of the same dog was precipitated with alcohol, there was a tendency for the renin solution so prepared from the normal kidney to become less active on standing, while that obtained from the ischemic kidney displayed either no significant change or some increase in its pressor activity on standing (fig 2 *B* and *C*)

Since the renin solution made by Pickering and Prinzmetal³ had been prepared by precipitation with 2 volumes of alcohol, while the results mentioned in this study had been obtained with fractions prepared by precipitation with 10 volumes of alcohol, the following experiment was performed. The normal and the ischemic kidney of a dog in which unilateral renal ischemia had been produced by means of a Goldblatt clamp were divided into two equal parts, one of which was ground into 1½ volumes and the other into 10 volumes of alcohol. The mixtures thus obtained were then filtered, washed with ether, dried, extracted with a solution of sodium chloride and tested on 3 rats. The kidneys were ground into the alcohol within less than one

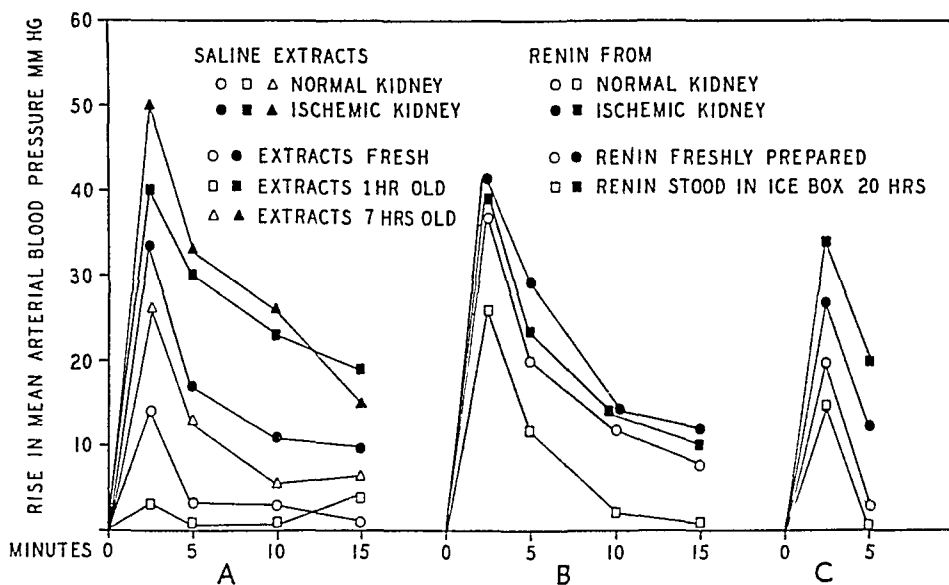


Fig 2—Comparison of pressor properties of the normal and the ischemic kidneys of Goldblatt dogs. The results of three different experiments are shown, each curve representing the average value on 2 to 4 rats. (*A*) Saline extract from the normal kidney of a dog with unilateral ischemia first became less active and then more active. Similar extract from the ischemic kidney showed a progressive increase in pressor effect. (*B*) On standing the renin solution from the normal kidney became less active, while that from the ischemic organ showed only a slight change. (*C*) Although the changes were slight, the renin solution from the normal kidney became less active on standing, and the reverse change occurred in the fraction from the ischemic kidney.

minute after removal from the body, and the renin solution was injected into the rats within five minutes after the solution of sodium chloride had been added to the dry powder. The various fractions were tested immediately after preparation and again after standing in the ice box for twenty-four hours. The results of this experiment are shown in figure 3. The freshly prepared extracts from this dog displayed practically no difference between the normal and the ischemic kidney, although the pressor effect of the renin prepared by precipitation with 10 volumes of alcohol was markedly greater than that made by precipitation with 1½ volumes

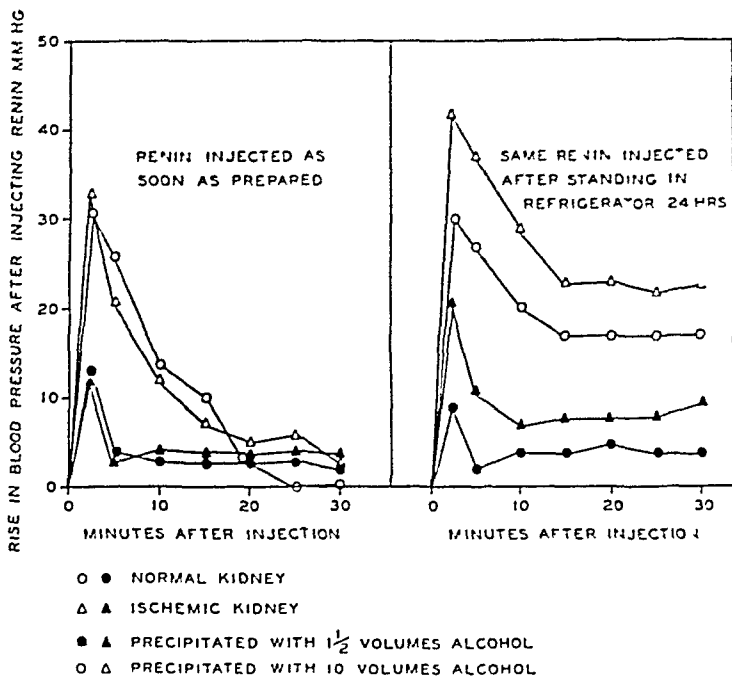


Fig 3—Fractions of renin freshly prepared by precipitation either with 10 or with $1\frac{1}{2}$ volumes of alcohol from the normal and the ischemic kidneys were practically identical as regards pressor effect. However, after the same solutions had stood in the ice box for twenty-four hours the fractions from the ischemic kidney were decidedly more active. Each curve represents the average value for 3 rats.

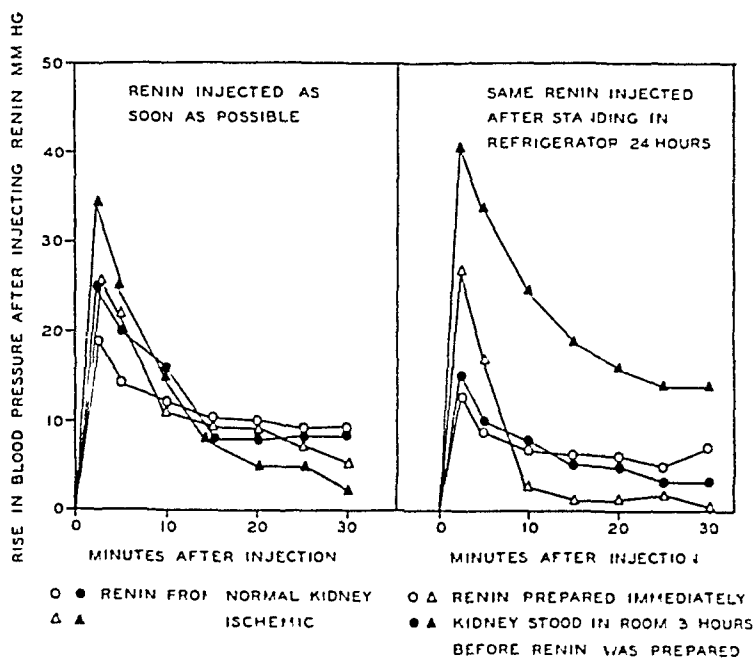


Fig 4—Renin solutions prepared from portions of the normal and the ischemic kidney as soon as possible after removal from the living animal had less pressor effect than did similar solutions prepared from the remaining portions of the same kidneys which had been allowed to stand in the room for three hours. After these same renin solutions had been kept in the ice box for twenty-four hours the pressor effect of the extracts from the normal kidneys diminished, while the effect of those from the ischemic kidneys increased. In all instances the fractions from the ischemic kidney had greater activity than the similarly prepared fractions from the normal kidney of the same dog. Each curve represents the average value for 3 rats.

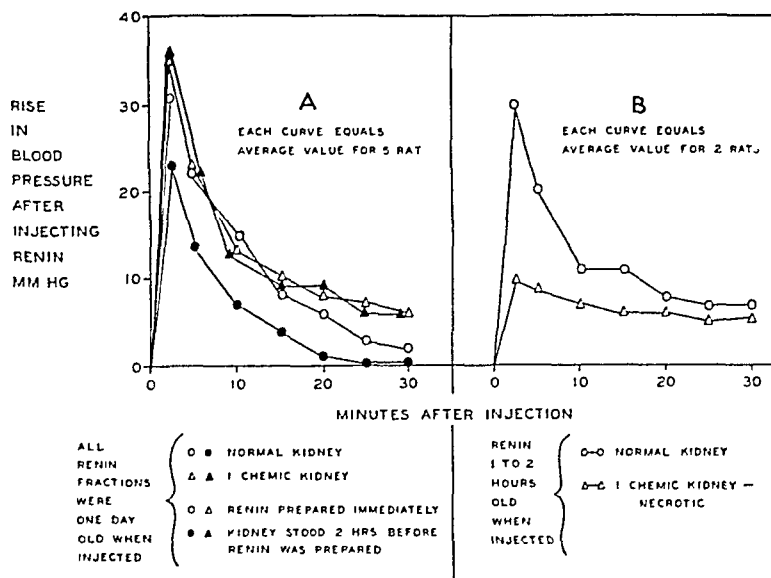


Fig 5—(A) One half of each kidney was ground into alcohol immediately, the other half being allowed to stand in the room for two hours before being treated with alcohol. The normal kidney lost pressor effect on standing. No significant change occurred in the ischemic kidney. (B) When the Goldbatt clamp was applied so snugly as to produce necrosis, the necrotic kidney had decidedly less pressor effect than did the normal organ from the same dog. This suggests that renin is not simply a degradation product of autolytic processes.

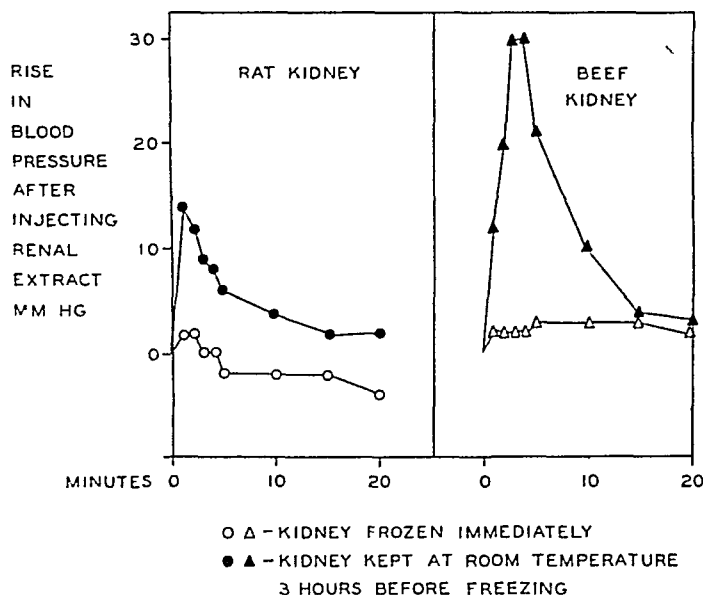


Fig 6—In these two experiments the extracts from kidneys frozen in liquid air as soon as they were removed from the body and subsequently dried at -30°C had practically no pressor effect. Similarly prepared extracts from kidneys which were allowed to stand in the room three hours before freezing had definite pressor action. (Results such as these were not regularly obtained, for in some experiments a well marked rise in blood pressure was produced by extracts of kidneys frozen immediately [fig 7])

After standing in the ice box overnight the pressor effects of the two fractions from the normal kidney were practically unchanged. However, the fractions from the ischemic kidney displayed a noticeably greater pressor effect than was observed on the preceding day (fig 3).

Since both the simple saline extracts and the more purified renin solutions showed an appreciable variation in their pressor activity as the result of standing, further experiments were performed in which half of a dog's kidney was ground into alcohol immediately after removal, the other half being allowed to stand in the room for several hours before it was ground with alcohol. In the experiment illustrated in figure 4, the extract of the ischemic kidney was found to have a slightly greater pressor effect than that from the normal kidney when the fractions were injected immediately after preparation, and in both instances the extracts of the kidneys which stood in the room for three hours before being treated with alcohol had a somewhat greater pressor effect than did the fractions prepared as

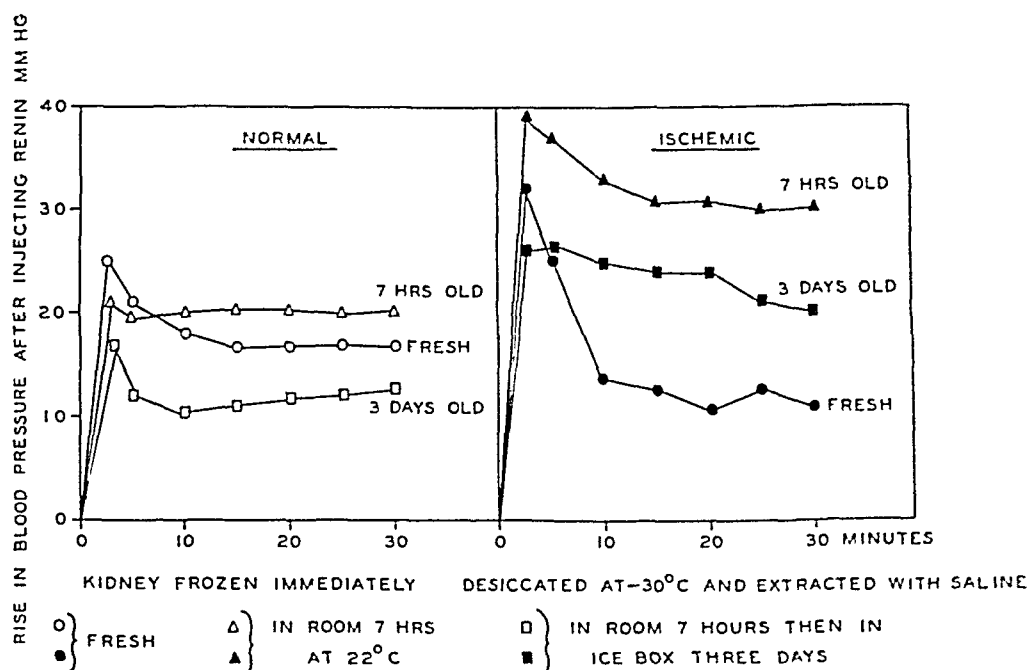


Fig 7—On standing seven hours the extract from the normal kidney displayed relatively little change in activity, while that from the ischemic kidney became much more active. After three days in the ice box both extracts had become less active. Each curve represents the average value for 3 rats.

soon as the kidney was removed from the body. The differences, however, were not striking with the freshly prepared fractions. On the other hand, when these same extracts, after having stood in the refrigerator for twenty-four hours, were tested again it was found that the extracts of the normal kidney had lost some of their pressor effect, while the fractions prepared from the ischemic kidney had a somewhat greater pressor effect than on the preceding day (fig 4). In another experiment carried out similarly it was observed that the extract from the normal kidney, on standing in the room, had become less pressor, while no significant change in the pressor activity of the ischemic kidney had occurred (fig 5 1).

The demonstration that the amount of renin present in a given extract often increases when the extract is allowed to stand, either in the room or in the ice box, naturally raises the question whether renin actually exists as such in the intact

kidney or whether it is an autolytic product of tissue disintegration. To determine whether autolysis *in vivo* causes an increase in renin content, 2 observations were made in which a Goldblatt clamp was deliberately applied so snugly to one renal artery that the vessel was almost completely occluded. Four days later the animal was killed, and the kidney was found to be necrotic. Renin solution was rapidly prepared from both the necrotic and the normal kidney by precipitation with alcohol, and in both instances the fractions from the former had much less pressor action than the similarly prepared fractions from the latter. One of these experiments is illustrated in figure 5B.

In order to eliminate as much as possible autolysis *in vitro*, kidneys were frozen in liquid air immediately on removal from the body and dehydrated *in vacuo* at -30 to -70°C . The desiccated powder thus obtained was extracted with a solution of sodium chloride and immediately injected into rats. In a number of experiments extracts so prepared had practically no pressor effect, while other extracts prepared from the same kidneys at room temperature produced the usual pressor response (figure 6). On the other hand, in some instances the fractions prepared by immediate freezing and desiccation produced well marked pressor responses (fig 7).

COMMENT

The results just presented demonstrate that the renal pressor substance designated by the term "renin" is highly unstable.⁶ The degree of pressor response produced by an extract of a given kidney alters appreciably with time. Fractions prepared in such a way as to reduce enzymatic processes to an absolute minimum frequently have no demonstrable pressor action. However, such extracts usually become highly pressor on standing for a short time at room temperature or for a number of hours in the ice box. On the other hand, fractions which are highly pressor may at times become much less so on standing. It seems clear that the renin content as determined by its pressor activity is highly variable. An increase in the apparent renin content may be explained as due to the formation of pressor substance from some precursor or to the disappearance of some depressor constituent of the extract. The disappearance of renin, on the other hand, may result from its destruction or inactivation, or the pressor effect of renin may

6 In this paper the term "renin" has been used to indicate the renal pressor substance. The recent work of Kohlstaedt, Helmer and Page (Kohlstaedt, K. G., Helmer, O. M., and Page, I. H. Activation of Renin by Blood Colloids, *Proc Soc Exper Biol & Med* **38** 214, 1938; Page, I. H. On the Nature of the Pressor Action of Renin, *J Exper Med* **70** 521, 1939) and of Braun-Menendez, Fasciolo, Leloir and Muñoz (Braun-Menendez, E., Fasciolo, J. C., Leloir, L. F., and Muñoz, J. M. *Rev Soc argent de biol* **15** 420, 1939; Braun-Menendez, E., and Fasciolo, J. C. *ibid* **15** 161, 1939) shows that renin is not in fact a direct pressor substance but is an enzyme which produces a pressor substance by acting on an activator contained in the blood serum. Since, however, the same investigators have shown that there is a general parallelism between the amount of renin injected and the rise in blood pressure produced, the validity of the conclusions which were arrived at would not be affected by the mechanism of renin action.

be masked by the production of depressor substances. It is not possible at present to state with certainty the exact mechanisms responsible for the spontaneous changes in the pressor effect of renal extracts.

The processes just mentioned appear to occur in both normal and ischemic kidneys. However, the general tendency in extracts of normal kidneys is for the pressor activity to diminish. In the ischemic kidney on the other hand, the pressor activity tends to increase.

Our experiments confirm those of Harrison, Blalock, Mason and Williams¹ and of Prinzmetal, Friedman and Abramson² in indicating that in the case of the dog extracts derived from the ischemic kidney usually have a more noticeable pressor effect than those from the normal kidney. Our observations on the kidneys of rats indicate that, as in the case of the rabbits studied by Pickering and Prinzmetal³ and of the rats studied by Beckwith and Chanutin,⁴ the normal kidney may have as much or more pressor activity than the abnormal kidney. However, in both the dog and the rat, extracts of the ischemic kidney tend to become more pressor on standing, while the general tendency in the case of the normal kidney is in the reverse direction, although extracts from the normal kidney may in time also become more active (figs. 1 and 2 *A* and *B*). The fundamental difference between the normal and the ischemic kidney appears to be in the rapid disappearance of the pressor activity in the normal organ and the increasing pressor activity in the ischemic organ.

The demonstration that ischemic kidneys differ from normal kidneys in their behavior as regards their renin content is compatible with the general view that renin may be concerned in the genesis of renal hypertension. Since this proposition is the subject of considerable discussion at present, it may be of interest to summarize some of the evidence for and against it.

The following observations suggest but do not prove that renin may play a role in the production of hypertension.

1. Ligation of both ureters of dogs usually causes a rise in blood pressure, removal of both kidneys does not.⁵

2. In a dog with hypertension due to ischemia of the sole remaining kidney nephrectomy is followed by a prompt decline of the blood pressure to a normal level.⁶

3. The data presented in this paper indicate that normal and ischemic kidneys may display distinct differences as to their enzymatic processes.

7. Harrison T. R., Mason M. F., Resnik H. and Rainey I. Changes in Blood Pressure in Relation to Experimental Renal Insufficiency. *Tr. A. Am. Physicians* **51**: 280, 1936.

8. Blalock A. and Levy S. E. Studies on the Etiology of Renal Hypertension. *Ann. Surg.* **106**: 826, 1937.

which produce and destroy renin (However, it has not yet been shown that renal hypertension induced by means other than by ischemia is associated with similar changes in the kidneys, and the available evidence ⁴ suggests that such may not be the case)

4 In hypertensive states there is generalized arteriolar contraction without change in the peripheral flow of blood ⁹ Renin seems to be the only known pressor substance which has such an action ¹⁰

5 Old rats are more sensitive to renin than young animals ⁵

6 Adrenalectomy, which often reduces the blood pressure of hypertensive animals,¹¹ causes normal animals to become less sensitive to renin ¹²

7 Pregnancy, which in hypertensive rats causes a marked decline in blood pressure, reduces the sensitivity of normal rats to renin ¹³

8 The administration of the renal antipressor substance, which produces a decline in the blood pressure of rats with renal hypertension, causes normal rats to become less sensitive to renin ¹³

9 Some authors have reported increased vasoconstrictor effects from perfusates of ischemic kidneys as compared with those of normal kidneys ¹⁴ (However, other workers have been unable to confirm their observations ¹⁵)

9 Prinzmetal, M , and Wilson, C The Nature of the Peripheral Resistance in Arterial Hypertension with Special Reference to the Vasomotor System, *J Clin Investigation* **15** 63, 1936

10 Landis, E M , Montgomery, H, and Sparkman, D Effects of Pressor Drugs and of Saline Kidney Extracts on the Blood Pressure and Skin Temperature, *J Clin Investigation* **17** 189, 1938

11 Goldblatt, H Studies on Experimental Hypertension Pathogenesis of Experimental Hypertension Due to Renal Ischemia, *Ann Int Med* **11** 69, 1937
 Blalock, A , and Levy, S E Studies on the Etiology of Renal Hypertension, *Ann Surg* **106** 826, 1937
 Page, I H Effect of Bilateral Adrenalectomy on Arterial Blood Pressure of Dogs with Experimental Hypertension, *Am J Physiol* **122** 352, 1938
 Collins, D A , and Wood, E H Experimental Renal Hypertension and Adrenalectomy, *ibid* **123** 224, 1938

12 (a) Williams, J R , Jr , Diaz, J T , Burch, J C , and Harrison, T R Relation of Adrenal Glands to Action of Renal Pressor Substance, *Am J M Sc* **198** 212, 1939
 (b) Friedman, B , Somkin, E , and Oppenheimer, E T The Relation of Renin to the Adrenal Gland, *Am J Physiol* **128** 481, 1940

13 Harrison, T R , Grollman, A , and Williams, J R , Jr The Antipressor Action of Renal Extracts and Their Capacity to Reduce the Blood Pressure of Hypertensive Rats, *Am J Physiol* **128** 716, 1940

14 Fasciolo, J C , Houssay, B A , and Taquini, A C The Blood-Pressure Raising Secretion of the Ischemic Kidney, *J Physiol* **94** 281, 1938

15 Mason, M F , and Rozzell, J D Attempts to Demonstrate Vasopressor Properties in the Serum of Hypertensive Dogs, *Proc Soc Exper Biol & Med* **42** 142, 1939

10 The blood of animals with experimentally produced renal hypertension contains an increased amount of renin activator ¹⁶

11 The amount of renin in the blood of the renal vein as estimated by studying the vasoconstrictor effect of blood to which a given amount of renin activator has been added, is increased in hypertensive animals

12 The hypertensive animal, like the nephrectomized animal, displays appreciable increase in sensitivity to renin ¹⁷

The following evidence opposes the view that renin is concerned in the genesis of hypertension

1 It is difficult to understand how persistent hypertension can be induced by a substance which when injected, repeatedly tends to lose its pressor effect

2 In acute experiments destruction of the spinal cords of rats ¹⁸ and of rabbits ¹⁹ with renal hypertension causes the blood pressure to decline to a level equal to that reached by normal animals after the same procedure, but renin still exerts a pressor effect in such animals. However, in more chronic experiments chordotomy does not abolish renal hypertension ²⁰

3 Extracts from either normal or ischemic kidneys prepared in such a way as to minimize enzymatic and autolytic processes have, in certain instances, exhibited practically no pressor effect

The evidence which has been cited in favor of the significance of renin is for the most part suggestive but not conclusive. Thus, the fact that hypertension usually occurs in middle-aged or elderly persons may not be in any way related to the increased sensitivity of senile rats to renin. Some authors have found ^{12a} that adrenalectomy does not lower the blood pressure of hypertensive animals until the general condition deteriorates seriously, and if so the decreased sensitivity of

16 (a) Kohlstaedt, K. G., Helmer, O. M., and Page, I. H. *Am Heart J*, to be published. (b) Page, I. H., and Helmer, O. M. Personal communication to the authors. (c) Page, I. H. Personal communication to the authors. (d) Braun-Menendez, E., Fasciolo, J. C., Leloir, L. F., and Muñoz, J. M. La substancia hipertensora de la sangre del riñón isquemado, *Rev Soc argent de biol* **15** 420, 1939.

17 (a) Braun-Menendez, E., and Fasciolo, J. C. Acción vasoconstrictora e hipertensora de la sangre venosa del riñón en isquemia incompleta aguda. *Rev Soc argent de biol* **15** 161, 1939. (b) Kohlstaedt, Helmer and Page ^{16a} Page ^{16c}

18 Dock, W., and Rytand, D. A. Absence of Vasoconstrictor Substance in Blood of Rats with Renal Hypertension, *Proc Soc Exper Biol & Med* **32** 374, 1934.

19 Dock, W. Personal communication to the authors.

20 Glenn, F., Child, C. G., and Page, I. H. The Effect of Destruction of the Spinal Cord on Hypertension Artificially Produced in Dogs. *Am J Physiol* **122** 506, 1938.

adrenalectomized animals to renin loses its significance. Finally, the renal antipressor substance inhibits not only the effects of renin but those of certain other pressor substances as well.¹³

In view of the conflicting nature of the work bearing on the subject, final conclusions concerning the role of renin in the genesis of renal hypertension cannot be justifiably drawn at present. The available evidence suggests that some pressor substance elaborated by the kidney may be concerned in the production of hypertension, but this has not yet been proved beyond cavil.

SUMMARY

Unilateral renal ischemia was produced in dogs and in rats. Fractions were prepared from such kidneys either by extraction with a solution of sodium chloride or by precipitation with alcohol, and their pressor action determined, with the following results:

1. The extracts from the ischemic kidney of a dog usually had a distinctly greater pressor effect than the similar extracts from the normal kidney of the same animal. When the degree of ischemia was so severe as to induce necrosis the abnormal kidney had less pressor effect than the normal organ.

2. The extracts from the normal kidney of a rat had as much or more pressor effect when compared with those of the ischemic kidney of the same animal, provided the fractions were tested soon after their preparation.

3. Kidneys from both rats and dogs displayed one important similarity. On standing the extracts from the normal kidney usually became less pressor and those from the ischemic organ tended to become more pressor.

4. When enzymatic processes were reduced to a minimum by rapid freezing and desiccation of the kidneys while frozen, the extracts in many instances had practically no pressor effect. However, such inactive, freshly prepared extracts if allowed to stand usually developed a well marked pressor action.

The divergent results obtained by previous investigators in regard to the relative pressor activity of normal and ischemic kidneys were apparently due to (a) difference in the species of animals used as a source of kidneys and (b) changes occurring in the activity of the extracts after preparation.

The apparent renin content of an extract (as measured by its pressor action) is extremely variable. It may increase or decrease with time and may even be absent under certain conditions.

Dr. Irvine Page allowed us to refer to some of his work which is still unpublished.

PRIMARY BACILLUS FRIEDLANDER (KLEBSIELLA PNEUMONIAE) PNEUMONIA

THERAPY OF B FRIEDLANDER B PNEUMONIA

ELY PERLMAN, M D *

AND

JESSE G M BULLOW A, M D

Clinical Professor of Medicine, New York University College of
Medicine, Visiting Physician, Harlem Hospital
NEW YORK

In 1882 Friedlander¹ described a gram-negative, encapsulated bacillus which was at first regarded as the cause of pneumonia. Four years later Weichselbaum² demonstrated that *Diplococcus pneumoniae* was the more frequent etiologic agent. Recent extensive studies show that *Bacillus Friedlander* causes about 0.5 to 4.0 per cent of all the pneumonias and accordingly will be encountered several times a year in any large medical service.

In 1925 Avery, Heidelberger and Goebel³ demonstrated the chemical and immunologic relationship of certain strains of this bacillus to *Pneumococcus* type II. The following year Julianelle⁴ classified a number of strains of *B. Friedlander* by immunologic methods under types A, B and C with a heterologous group X. There are now available the *Friedlander* bacillus A and the *Friedlander* bacillus B serum for identification of strains by the Neufeld technic, but the B strain also swells with the

* Littauer Fellow in Pneumonia Research

From the Medical Service, Harlem Hospital, Department of Hospitals, and the Littauer Pneumonia Research Fund of New York University College of Medicine.

This study received additional financial support from the Metropolitan Life Insurance Company and from Mr. Bernard M. Baruch. Mr. Bernard M. Baruch Jr., Miss Belle N. Baruch and Mrs. H. Robert Samstag.

1. Friedlander, C. Ueber die Schizomyceten bei der acuten fibrosen Pneumonie. *Virchows Arch. f. path. Anat.* **87**: 319, 1882.

2. Weichselbaum, A. Ueber die Aetiology der acuten Lungen- und Rippenabscessentzündungen. *Med. Jahrb.* **1**: 483, 1886.

3. Avery, O. T., Heidelberger, M. and Goebel, W. F. The Soluble Specific Substance of *Friedlander's* Bacillus. II. Chemical and Immunological Relationships of *Pneumococcus* Type II and of a Strain of *Friedlander's* Bacillus, *J. Exper. Med.* **42**: 709 (Nov.) 1925.

4. Julianelle, L. A. A Biological Classification of *Encapsulatus Pneumoniae* (*Friedlander's* Bacillus). *J. Exper. Med.* **44**: 113 (July) 1926.

type II pneumococcus typing serum It is important to determine the strain routinely, because only then can a better understanding of the disease, its management, its prognosis and its specific therapy be developed

It was shown by Avery, Heidelberger and Goebel³ that type II antipneumococcus horse serum was able to protect mice against what is now known as the B strain of B Friedlander Because no specific serum was available to us at the time of this study, we felt that type II antipneumococcus serum should be tried in the therapy of pneumonia due to B Friedlander B, especially in view of the high mortality In the case reported in this paper there were chosen from available type II antipneumococcus serums (horse and rabbit) those which, in highest dilution, produced capsule swelling when the patient's own strain of B Friedlander B was used The unitage of these serums in terms of their activity against B Friedlander B⁵ was estimated by Miss Frances L Clapp, of Lederle Laboratories, Inc The unitage is reported with the case history

REPORT OF A CASE

W S, a 33 year old Negro, was admitted on June 9, 1939 with a history of pleuritic pain in the right lower portion of the chest and chills beginning at 9 a m of the previous day The chills were soon followed by a severe cough productive of a moderate amount of tenacious, mucopurulent, blood-streaked sputum The patient vomited several times in the afternoon of that day and became dyspneic Physical examination revealed a well developed man who was acutely ill, dyspneic and restless There were marked dilatation of the alae nasi, congestion of the throat and slight edema of the eyelids The heart was normal Examination of the lungs showed dulness over the midportion of the right side of the chest posteriorly, with occasional crepitant rales and a friction rub at the angle of the right scapula The abdomen was normal The diagnosis was lobar pneumonia involving the upper and middle lobes of the right lung The temperature was 103.2 F and the pulse rate 124 per minute The blood count was 3,950,000 red cells, with a hemoglobin concentration of 65 per cent (Sahli) The white cell count was 17,500, with 73 per cent polymorphonuclear leukocytes and 24 per cent lymphocytes Chemical analysis of the blood showed creatinine 1.4 mg, urea 15 mg, sugar 130 mg and chlorides 410 mg per hundred cubic centimeters The Kahn reaction of the blood was 4 plus

On admission to the hospital the patient was too sick for a roentgen examination The first roentgenogram was taken on June 13 and was reported by Dr William Snow as follows "The chest shows consolidation of the upper lobe of the right lung, with scattered patches in the base of the right lung and the mid-

5 In a recent paper, Beeson and Goebel (*J Immunol* **38** 231 [March] 1940) stated that type II antipneumococcus rabbit serum gave none of the protection or other immunologic cross reactions against B Friedlander B which type II horse serum gave Experiments done in this laboratory indicate that the difference between horse and rabbit serum in this regard is one of degree In a comparison of horse and rabbit serums of equal type II mouse-protection unitage, the horse serum is found to be approximately fifteen to thirty times as active against B Friedlander B as rabbit serum

portion of the left lung" The sputum showed B Friedlander B, and the organism grew in cultures of blood taken at 10 30 a m and at 12 noon of the first day of hospitalization The patient was extremely ill and coughed up large amounts of sputum typical of that seen in cases of pneumonia due to B Friedlander, i e, of extremely tenacious and markedly and diffusely bloody character The cough became progressively worse and more productive, the patient bringing up 1 to 2 ounces (30 to 60 cc) of material about every five minutes The patient was regarded as having the acute fulminating type of Friedlander pneumonia

Treatment was begun three hours after admission Five grams of sulfapyridine (2-[paraaminobenzenesulfonamido] pyridine) was given as the initial dose, followed by 1 Gm every four hours day and night Serum therapy was begun at the same time, over a period of twenty-four hours the patient was given a total of 594,000 units of type II antipneumococcus horse and rabbit serums The estimated unitage of these serums indicated that the patient actually received about 25,000 units in terms of the Friedlander B bacillus

A sample of blood taken on June 12 showed no free capsular polysaccharide when a type II antipneumococcus rabbit serum was used A 1 2 dilution of the patient's serum in physiologic solution of sodium chloride gave a 3 plus agglutination reaction⁶ with a type II suspension and a 3 plus precipitation reaction⁶ with a solution of type II capsular polysaccharide The study was done by the method described by Bukantz, Bullowa and de Gara⁷

Course—During the first two days the patient's course was rapidly downhill By morning of the third day, though the temperature remained elevated, the patient began to show clinical signs of improvement The administration of sulfapyridine was continued, and because of the delay of defervescence, on the afternoon of June 13 (the fifth day of hospitalization) 50 cc of a 10 per cent solution of sulfapyridine in 50 per cent dextrose⁸ was administered intravenously, followed in twenty-four hours by 5 Gm of sulfapyridine sodium dissolved in 50 cc of physiologic solution of sodium chloride, given in the same manner The temperature dropped to 100 F and continued to hover between 100 and 101 F The diagnosis of pleural effusion in the right side of the chest was made and confirmed by a thoracic tap, performed on June 18, which yielded 25 cc of a clear, yellow, sterile fluid A roentgenogram showed two separate collections of fluid, and the patient's chest was again tapped on June 20 Six hundred cubic centimeters of fluid was removed, which was sterile Two successive thoracic taps yielded progressively thicker fluids, which remained sterile

6 A 3 plus reaction is one in which a definite "button" appears but can be slightly broken up by vigorous agitation

7 (a) Bukantz, S C, Bullowa, J G M, and de Gara, P F Detection of Free Polysaccharide in Blood of Pneumococcic Pneumonia Patients Prognosis and Therapy, *Proc Soc Exper Biol & Med* **41** 250 (May) 1939 (b) The studies of Dochez and Avery (Soluble Substance of Pneumococcus Origin in the Blood and Urine During Lobar Pneumonia, *ibid* **14** 126 [March] 1917) demonstrated that the employment of specific precipitation tests with immune serums on patients with pneumococcic pneumonia was a procedure of diagnostic as well as prognostic significance Blake (Antigen-Antibody Balance in Lobar Pneumonia, *Arch Int Med* **21** 779 [June] 1918) first demonstrated the presence of a positive precipitin reaction in the urine of a patient with pneumonia due to the Friedlander bacillus when the urine was tested with specific antiserum

8 A special preparation supplied by Lederle Laboratories, Inc

greater protection against Friedlander infections was induced by sulfapyridine than by sulfanilamide, as indicated by a longer period of survival and an occasional recovery. Sulfapyridine apparently cured a patient with "repeated B. Friedlander sepsis," type undetermined, secondary to bronchitis (Meyer and Amtman¹²). In view of these findings and the apparently successful use of sulfapyridine in the case we have reported in detail, a review was made of all the proved cases of Friedlander pneumonia recorded at Harlem Hospital since the report of Bullowa, Chess and Friedman,¹³ which included the cases from July 1, 1929 through June 30, 1936. The present study includes cases from July 1, 1936 through Dec. 31, 1939. The clinical classification used is the same as that in the first report.

The criteria used for the diagnosis of Friedlander pneumonia are indicated in table 1 for each case. All doubtful cases were excluded. The difficulty of deciding whether the organisms found in the sputum are carriers or are pathogenic is no greater for the Friedlander than for the pneumococcal pneumonias. The carrier incidence of an organism is no criterion of its pathogenicity. The reported carrier incidence of the Friedlander bacillus varies from 5.8¹⁴ to 25 per cent. In a large group of patients with miscellaneous infections of the upper respiratory tract studied in our service, the carrier incidence of the Friedlander bacillus was 2.2 per cent, as compared with a carrier incidence for pneumococci of 69 per cent.¹⁵ With the exception of a few cases, the criteria for the diagnosis of Friedlander pneumonia as set forth by Baehr, Schwartzman and Greenspan¹⁵ were satisfied, and, as far as possible, sources of infection other than the lung were excluded. We considered a patient to be suffering from Friedlander pneumonia when there were significant combinations of the following findings: definite clinical and roentgenologic evidence of pulmonary consolidation, repeated presence of the Friedlander bacillus and absence of other etiologic organisms in the sputum, positive blood cultures, identification of the organism in antemortem or postmortem aspirates from the lung, and presence of specific capsular polysaccharide in the blood or in the urine or in both. When both a Friedlander bacillus and a pneumococcus were found in the same case, the case was excluded, unless, as in case 18 (table 1), there was conclusive evidence that the bacillus was the causative organism.

12 Meyer, K. A., and Amtman, L. Treatment of Friedlander's Septicemia by Sulfapyridine, with Recovery, *J. A. M. A.* **113** 1641 (Oct. 28) 1939.

13 Bullowa, J. G. M., Chess, J., and Friedman, N. B. Pneumonia Due to *Bacillus Friedlander*, *Arch. Int. Med.* **60** 735 (Nov.) 1937.

14 Bloomfield, A. L. The Mechanism of the Bacillus Carrier, with Special Reference to the Friedlander Bacillus, *Am. Rev. Tuberc.* **4** 847 (Jan.) 1921.

15 Baehr, G., Schwartzman, G., and Greenspan, E. B. *Bacillus Friedlander* Infections, *Ann. Int. Med.* **10** 1788 (June) 1937.

TABLE 1—Data Concerning Thirty-Seven Patients with Friedlander's Pneumonia

Case Number	Initials	Race	Date of Admission	Sex	Age, Years	Lobes Involved *	Sputum Typing +	Blood Culture	Clinical Classification of the Pneumonia	Therapy +	Day of Disease on Which Therapy Was Given	Day of Disease on Which Death Occurred	Elapsed Time Between Treatment and Death	Comment
1	H H	N	Feb 1937	M	36	R L L	+M P	—	Acute fulminating	307,500 units B F A horse serum	3d	3d	8 hr	Postmortem cultures of lung puncture fluid and heart blood positive for B F A
2	A J	N	June 1937	F	23	R U L	+M B	—	Subacute	None	Lived	Lived		Spontaneous recovery with crisis on 11th day
3	C L	N	Dec 1936	M	35	L L L	+Sp	—	Acute fulminating	217,500 units B F A horse serum	2d	3d	24 hr	Antemortem cultures of lung puncture fluid negative, postmortem cultures of lung puncture fluid and heart blood positive for B F A
4	J M	N	Aug 1936	M	43	R L L	+M P	+	Acute fulminating	84,000 units B F A horse serum	2d	2d	7 hr	Antemortem culture of lung puncture fluid positive for B F A
5	C N	N	June 1937	M	33	R M L	+M B	+	Acute	720,000 units B F A horse serum	6th	8th	24 hr	Blood culture on June 25 positive, blood culture on June 26 negative temporary response to therapy ?
6	J S	N	Feb 1937	M	51	R L L	+Sp	—	Acute fulminating	58,500 units B F A horse serum	3d	3d	3 hr	Postmortem culture of lung puncture fluid and heart blood negative
7	O W	N	May 1937	M	66	R U L	—	—	Acute	453,000 units B F A horse serum	5th	6th	26 hr	Antemortem culture of lung puncture fluid positive for B F A
8	J T	N	Dec 1936	M	60	R L L	—	+	Acute	None		10th		Postmortem cultures of pericardial fluid positive for B F A
9	R R	N	Jan 1938	M	30	R U L	—	—	Acute	None		9th (?)		Death 2 hr after admission, postmortem culture of heart blood positive for B F A
10	R A	N	March 1938	M	56	R U L	+Sp	—	Acute fulminating	510,000 units B F A horse serum	2d	3d	25 hr	Postmortem culture of lung puncture fluid and heart blood positive for B F A
11	J B	N	Jan 1938	M	43	R U L	+M P	—	Acute fulminating	35,000 units B F A horse serum	4th	4th	1 hr	Postmortem culture of lung puncture fluid positive for B F A
12	S B	W	Aug 1937	M	40	L L L	+Sp	+	Acute	285,000 units B F A horse serum	12th	12th	4 hr	Postmortem culture of lung puncture fluid and heart blood positive for B F A
13	T Q	W	Aug 1937	M	41	R L L	+Sp	—	Acute	613,000 units B F A horse serum	4th to 10th	12th	2 days	Antemortem culture of lung puncture and thoracic tap fluid positive for B F A
14	D O	N	Oct 1938	M	52	R U L	+Sp	—	Acute	Unknown unitage, B F A rabbit serum	3d	5th	2 days	Postmortem culture of lung puncture fluid positive for B F A
15	J M	N	April 1939	M	35	L L L	+Sp	—	Acute fulminating	5 Gm Sp	2d	2d	1 hr	
16	W J	N	April 1939	M	73	R L L	+M P	—	Acute	11 Gm Sp	?	?	4 hr	Cardiac disease with terminal pneumonia
17	J B	N	March 1939	M	59	R U L	+Sp	—	Chronic	None		?		First admission 9 mo previously with B F A pneumonia, recovered with no treatment, of lung fluid positive for B F A
18	R M	N	Aug 1938	M	40	R U L	+Sp	+	Acute fulminating	14 Gm S, type XIV serum	5th	Lived		Type XIV pneumococcus and B F A found on direct sputum typing antemortem culture of lung puncture fluid positive for B F A only SSS for both B F A and type XIV pneumococcus found in urine
19	H S	N	March 1939	M	52	R M L	+Sp	+	Acute fulminating	1 dose B F A rabbit serum	4th	4th	10 min	Patient in terminal stage on admission

20	P C	W	April 1939	M	63	R L L R M L	+Sp	+	Acute fulminating	6 Gm Sp	2d	2d	3 hr	Patient with chronic alcoholism in terminal stage on admission
21	J B	N	March 1939	M	61	R L L	+Sp	—	Acute fulminating	2 doses B F A rabbit serum	?	?	3 hr	Postoperative pneumonia, intestinal obstruction
22	L F	N	Aug 1939	M	66	R U L R L L	+Sp	—	Acute fulminating	65 Gm Sp, 60 cc B F A rabbit serum	2d	6th	4 days	Temporary response to therapy (?)
23	J W	N	Feb 1939	M	40	L U L	+M P	—	Acute fulminating	11 Gm Sp, 64 cc B F A rabbit serum	2d	2d	1 hr	
24	G V	N	Sept 1939	M	52	R L L	+Sp	—	Acute fulminating	None	5th	5th	30 min	Death too soon after admission to permit institution of therapy
25	I R	N	Oct 1939	M	42	R L L	+Sp	—	Acute fulminating	3.5 Gm Na Sp i v, 9 Gm Sp	1st	1st	3 hr	Postmortem culture of heart blood positive for B F A
26	T D	N	Nov 1939	M	57	L L L	+Sp	—	Acute fulminating	84 Gm Sp, 10 Gm Na Sp i v	1st	Lived		Development of empyema, culture of chest fluid positive for B F A, disappearance of B F A S S S in chest fluid after appearance of antibodies in patient's blood
27	A L	N	Nov 1939	M	41	R U L	+Sp	—	Acute	None		7th (?)		Postmortem culture of lung puncture fluid positive for B F A
28	C J	N	Dec 1939	M	78	L L L	+M P	—	Acute fulminating	7 Gm Sp	?	?	9 hr	Pneumonia following a prolonged drinking bout
29	M T	N	Nov 1939	M	40	R L L	+Sp	—	Subacute to chronic?	27 Gm Sp	4th	Lived		Temperature dropped to below 100 F seven days after institution of therapy
1	C J	N	June 1939	M	49	R L L	+Sp	+	Acute fulminating	Friedlander B Pneumonia 600,000 units type II horse serum, 28 Gm Sp	3d to 5th	6th	30 hr	Sp (10 Gm) given intravenously
2	C P	N	Dec 1937	F	27	R U L R M L R L L	+M P	+	Acute	None		Lived		Antemortem culture of lung puncture fluid positive for B F B, spontaneous crisis on 11th day
3	M M	N	Sept 1938	F	32	R L L L L L	+Sp	+	Acute fulminating	5 Gm Sp	2d	3d	32 hr	
4	S B	N	July 1939	M	51	R L L	+Sp	+	Acute	187,000 units type II rabbit serum,	4th	10th	6 days	Post traumatic pneumonia, postmortem culture of peritoneal fluid positive for B F B
5	R S	W	Oct 1939	F	52	L L L	+Sp	—	Acute fulminating	14 Gm Sp 89 cc B F B rabbit serum, 16 Gm Sp, 10 Gm Na Sp i v	1st	2d	20 hr	
6	G B	N	Oct 1939	M	54	R U L R M L R L L	+Sp		Acute fulminating	100 cc B F B rabbit serum, 18 Gm Sp, 10 Gm Na Sp i v	1st	3d	2 days	
7	W S	N	June 1939	M	33	R U L R M L R L L	+Sp	+	Acute fulminating			Lived		See case report in text
8	M D	N	Dec 1939	F	22	L L L	+M B	—	Acute fulminating	None		?		Patient in alcoholic coma when admitted to hospital, death 30 hr after admission

* The following abbreviations are used in describing the lobes involved: R L L, lower lobe of the right lung, R U L, upper lobe of the right lung, L L L, lower lobe of the left lung, R M L, middle lobe of the right lung, and L U L, upper lobe of the left lung.

† The following abbreviations are used in distinguishing the methods of typing sputum: +M P, sputum typing obtained from peritoneal fluid of a mouse given an injection of sputum; +M B, sputum typing obtained from mouse brain culture, and +Sp sputum typing obtained directly.

§ S S S indicates presence of specific capsular polysaccharide.

‡ The following abbreviations are used in distinguishing therapeutic agents: Sp, sulfapyridine, S, sulfanilamide, Na Sp, i v, sulfapyridine sodium given intravenously, B F, B Friedlander, B F A, B Friedlander A, and B F B, B Friedlander B.

INCIDENCE

In the present series, which included cases from July 1, 1936 through Dec 31, 1939, there were 2,450 cases of pneumonia, in 37 (1.5 per cent) of which the causative organism was the Friedlander bacillus and in 29 (1.2 per cent) of which it was *B. Friedlander* A. In 8 (0.5 per cent) of the last 1,750 cases of this series the disease was due to *B. Friedlander* B. The figures for Friedlander B pneumonia are exclusive of those for the year June 1936 to June 1937, during which time Friedlander B organisms were not typed and classified as such, all Friedlander bacilli not of the A type were left unclassified.

The reported incidence of Friedlander pneumonia varies between 0.4 and 13 per cent. Heffron,¹⁶ in a summary of the findings in three reports, noted an average incidence of 0.5 per cent in a total of 3,319 cases of pneumonia. Bullowa,¹⁷ in a study of 4,416 cases of pneumonia, noted that the cases of Friedlander pneumonia comprised 1.1 per cent of the total. Of 100 cases of pneumonia studied in India by Bhatnagar and Singh,¹⁸ the Friedlander bacillus was the etiologic agent in 13 per cent. Solomon¹⁹ noted an incidence of 0.6 per cent in a review of 5,000 cases, but the incidence was 4.0 per cent in the 300 cases studied carefully.

The relative incidence of Friedlander A pneumonia and Friedlander B pneumonia is similar to that reported by Julianelle, who in his first study⁴ reported that the A strain caused 70 per cent of the Friedlander pneumonias. In a later study²⁰ he showed that in a mixed group of 54 cases of general infections caused by the A and the B strain of *B. Friedlander* the former was the causative agent in 78 per cent and the latter in 22 per cent, however, of 45 of his cases of Friedlander pneumonias, the A strain was causative in 33, the B strain in 2 and the C strain in 3, in 7 cases the organisms fell into the unclassified group X. Cooper²¹ reported that in 95 per cent of cases Friedlander pneumonia

16 Heffron, R. *Pneumonia, with Special Reference to Pneumococcus Lobar Pneumonia*, New York, The Commonwealth Fund, 1939.

17 Bullowa, J. G. M. *The Management of the Pneumonias*, New York, Oxford University Press, 1937.

18 Bhatnagar, S. S., and Singh, K. *Bacteriological Studies in Acute Lobar Pneumonia Due to Pneumococcus and B. Pneumoniae Friedlander*, *Indian J. M. Research* **23** 337 (Oct.) 1935.

19 Solomon, S. *Primary Friedlander Pneumonia*, *J. A. M. A.* **108** 937 (March 20) 1937.

20 Julianelle, L. A. *The Distribution of Friedlander's Bacilli of Different Types*, *J. Exper. Med.* **52** 539 (Oct.) 1930.

21 Cooper, cited by Solomon,¹⁹ p. 940.

was due to the A strain. In the present series of 37 cases, the A strain was present in 29 (79 per cent) and the B strain in 8 (21 per cent).

Friedlander pneumonia occurs predominantly in older people, as can be readily seen from the following summary:

Series	No. of Patients	Patients Over 40
Bullowa, Chess and Friedman ¹³	41	29
Solomon ¹⁹	32	26
Present series	37	26

The mortality is higher in the older age groups, and although the number of cases is insufficient for accurate judgment, there appears to be a tendency for the Friedlander B organism to attack younger persons:

B Friedlander A	22 patients 40 years or over (20 died)
	7 patients under 40 years (5 died)
B Friedlander B	4 patients 40 years or over (4 died)
	4 patients under 40 years (2 died)

As happens in most types of the pneumococcic pneumonias, pneumonia caused by B Friedlander occurs much more frequently in men than in women. Both Solomon ¹⁹ and Bullowa, Chess and Friedman ¹³ found that seven times as many men as women suffered from Friedlander pneumonia. In the present series of 37 cases, 32 patients were men and 5 were women, a ratio of approximately 7 to 1. However, an interesting fact comes to light when the pneumonia in this series is classified according to type. Of 29 patients with Friedlander A pneumonia 28 were men, a ratio of 28 to 1, and of 8 patients with Friedlander B pneumonia 4 were men and 4 were women, a ratio of 1 to 1.

When the modification of the chi square test especially designed for small samples is applied, there is a high significance for the difference in the ratio of men to women in the A and the B groups, respectively. The probability of the distribution actually observed being due to pure chance is exceedingly small, namely, 0.005, which indicates with practical certainty that there is a definite connection between sex and the occurrence of Friedlander A pneumonia ²².

BACTEREMIA

In the present study, cultures of the blood were made routinely at the time of the patient's admission to the hospital and were followed, in most cases, by another just before the institution of therapy. Subsequent cultures of the blood were made if the first cultures were positive for the organism, if the patient remained ill or if the patient became worse after admission.

²² Dr. Alfred J. Lotka, of the Metropolitan Life Insurance Co., provided this analysis.

The reported incidence of bacteremia averages about 70 per cent²³ The general incidence (A and B forms) in the present series was much lower, 32.5 per cent. An interesting difference in tendency to bacteremia in the two types was noted. Seven of the 29 patients with Friedlander A pneumonia (24 per cent) and 5 of the 8 patients with Friedlander B pneumonia (62.5 per cent) had bacteremia.

When the statistical method already used was applied, the probability p was found to be 0.014. Any value for p below 0.05 was considered to be statistically significant. However, the probable error in each group was increased by such factors as the day of illness on which the culture of the blood was made and the number of cultures made. Another fact tending to minimize the significance of the difference was the discrepancy between the low incidence of bacteremia for Friedlander A and B pneumonias as found in this study and that reported by other authors.

TABLE 2—*Mortality Rates for Friedlander Pneumonias*

Authors	Number of Patients	Percentage of Mortality
Solomon ¹⁹	32	97
Bhatnagar and Singh ¹⁸	13	92
Cole, R. I. Acute Pulmonary Infections, DeLa Mar Lectures, Johns Hopkins University School of Hygiene and Public Health, 1927-1928	7	71
Bullowa ¹⁷	39	82 *
Bullowa, Chess and Friedman ¹³	41	83 †
Present series	37	84

* Untreated patients

† Untreated and treated patients combined

MORTALITY

The mortality is consistently high among patients with Friedlander pneumonias. The mortality reported by the various authors is shown in table 2.

The mortality among the patients with Friedlander A and with Friedlander B pneumonia in the present series did not differ significantly, being 86 per cent among the former and 75 per cent among the latter.

Solomon¹⁹ pointed out what is implicit in the data of the other authors cited, namely, that there is no relationship between bacteremia and mortality. (This conclusion may be modified if cultures of the blood are made more frequently.) Indeed, the patients in the present series without bacteremia had a somewhat higher mortality than those with bacteremia. This relationship can be seen in table 3 which also shows the mortality for the two types of Friedlander pneumonia.

23 Bullowa, Chess and Friedman¹³ Bullowa¹⁷ Solomon¹⁹

TREATMENT

Bullowa, Chess and Friedman¹³ reported a mortality of 50 per cent for patients with Friedlander A pneumonia who were treated with specific antipneumococcus horse serum. This mortality was contrasted with that of 94 per cent for the untreated patients. All of the 5 patients whom Solomon¹⁹ treated with horse serum died. However, Solomon used smaller amounts of serum in all but 1 case, and therefore the results

TABLE 3—*Mortality Rates for Two Types of Friedlander Pneumonia, Both With and Without Bacteremia, in Present Series*

	Number of Patients	Number Died	Percentage of Mortality
Friedlander A pneumonia			
Bacteremia	7	6	86
No bacteremia	22	19	86
Total	29	25	86
Friedlander B pneumonia			
Bacteremia	5	3	60
No bacteremia	3	3	100
Total	8	6	75
Combined group (Friedlander A and Friedlander B pneumonias)			
Bacteremia	12	9	75
No bacteremia	25	22	88
Total	37	31	84

TABLE 4—*Results of Treatment of Friedlander A and B Pneumonias in Present Series*

	SP *		SP * and Serum		Serum Alone		No Treatment	
	Patients	Deaths	Patients	Deaths	Patients	Deaths	Patients	Deaths
Friedlander A Pneumonia								
Total	8	5	2	2	13	13	6	5
Without bacteremia	6	4	2	2	9	9	5	4
With bacteremia	2	1	0	0	4	4	1	1
Friedlander B Pneumonia								
Total	1	1	5	4			2	1
Without bacteremia	0	0	2	2			1	1
With bacteremia	1	1	3	2			1	0

* SP indicates sulfanilamide or sulfapyridine, as indicated in table 1

are not comparable. The results of the therapy in the present series, including those in patients treated with sulfanilamide or sulfapyridine, are shown in table 4.

Of 23 treated patients with Friedlander A pneumonia, 6 of whom had bacteremia, 20 died, and of 6 untreated patients, 1 of whom had bacteremia, 5 died.

Of the patients with Friedlander A pneumonia treated with serum alone 3 received rabbit serum and 10 horse serum. All these patients

died. However, if there is any greater advantage in the use of rabbit serum, it could not be ascertained from this group, since those patients who were given rabbit serum died too soon after admission to have received an adequate amount.

Of 6 treated patients with Friedlander B pneumonia, 4 of whom had bacteremia, 5 died, and of 2 untreated patients, 1 of whom had bacteremia, the patient without bacteremia died. The details of therapy are given in table 1.

Administration of serum, sulfanilamide (or sulfapyridine) or the two combined seemed ineffectual in treating patients with B Friedlander pneumonia in our series. Indeed, among the patients with Friedlander B pneumonia, the mortality of the treated ones was 83 per cent and the mortality of the untreated ones 50 per cent. One hopeful trend could be seen in the patients with Friedlander A pneumonia, for treatment with the drug was accompanied by recovery in 3 of 8 cases.

COMMENT

That there is no relationship between bacteremia and mortality was indicated in Solomon's report and in the present study. Baehr, Schwartzman and Greenspan¹⁵ reported transient bacteremia from the genitourinary tract and elsewhere in patients who recovered spontaneously. It was shown²⁴ that the presence of specific capsular polysaccharide in the blood stream of patients with pneumococcal pneumonia has a far more serious prognosis than the finding of bacteremia alone in such patients, especially in pneumonias caused by *Pneumococcus* type III. The Friedlander bacillus, like the type III pneumococcus, has a huge capsule and produces much polysaccharide. These facts suggest that in cases of Friedlander pneumonia, the presence of a small or avirulent focus with the simple transient occurrence of bacteremia is relatively innocuous as compared with the presence of a large or virulent focus of infection, with or without the occurrence of bacteremia.

Several observers¹⁶ expressed the opinion that even the relatively low incidence reported for pneumonia due to Friedlander bacillus is too high, because the organism is a frequent contaminant and therefore is too often erroneously considered the etiologic agent. In Solomon's experience the reported incidence is too low. That the Friedlander bacillus is not a pregonal invader or a postmortem contaminant is amply borne out by the fact that, without exception, we have never found

24 Bullowa, J. G. M., Bukantz, S. C., and de Gara, P. F. The Balance Between Capsular Polysaccharide and Antibody in Relation to the Prognosis and Therapy of Pneumococcal Pneumonia, *Ann Int Med* **14** 1348 (Feb) 1941. Bullowa, Bukantz and de Gara^{7a}

Friedlander organisms in many hundreds of preagonal and postmortem cultures of the blood and of puncture fluid from the lungs. Nor has this bacillus, in our experience, been found as a contaminant in cultures taken from lung tissue at the autopsy table. We have had one epidemic of infections caused by Friedlander bacillus in the mice used for sputum typing, which resulted in a few false diagnoses, but it was quickly apprehended and the diagnoses corrected.

The success of serum therapy depends on the early administration of a "sufficient" amount of specific serum. Certain of the types of pneumococci, for example types II and III, produce large amounts of specific capsular polysaccharide, successful serum therapy of pneumonias caused by these types depends on the administration of comparatively larger amounts of serum than is required for pneumonias caused by the other types. Reasoning by analogy, we assumed that since Friedlander organisms produce a large amount of specific capsular polysaccharide, the treatment of infections caused by *B. Friedlander* requires relatively larger amounts of serum to neutralize this substance. Indeed, the relatively massive amounts of serum given in several of the aforementioned cases may have been ineffectual because they were still insufficient. Certainly, the amount of type II antipneumococcus serum given in the case of Friedlander pneumonia reported was insufficient, unless it was just the amount needed to supplement the effect of the sulfapyridine and the patient's own immunity and so swing the balance in favor of the host.

Only 2 patients with chronic Friedlander pneumonia were seen, 1 recorded as case 17 and another not included in the series because he was admitted to the service after January 1940. Both patients had mild diabetes. These were the only patients with diabetes in the series. Both died with extensive cavitations.

SUMMARY

A case of Friedlander *B.* pneumonia with apparent cure is reported. Therapy is discussed.

A review of 37 cases of pneumonia due to Friedlander bacillus is presented, and the available statistics are summarized.

B. Friedlander B. is immunologically related to *Pneumococcus* type II, and type II antipneumococcus serum may be of value in the specific treatment of Friedlander *B.* pneumonia.

The lack of relationship of bacteremia to mortality is pointed out.

The inadequacy of the various forms of therapy used is noted.

The Friedlander organism, in our experience, is not a contaminant or a preagonal invader.

Seven times as many men as women have Friedlander pneumonia. However, the ratio of men to women with Friedlander A pneumonia is 28 to 1, as compared with the ratio for Friedlander B pneumonia, which is 1 to 1. This is a statistically significant difference in sex incidence. The incidence of bacteremia is probably significantly higher in cases of Friedlander B pneumonia than in those of Friedlander A pneumonia. The differentiation between Friedlander A and Friedlander B pneumonia should always be made in the interest of a better understanding of the disease and the institution of more rational therapy.

USE OF SULFANILAMIDE AND SULFAPYRIDINE IN THERAPY OF SUBACUTE BACTERIAL ENDOCARDITIS

MEYER FRIEDMAN, M D

WITH THE COLLABORATION OF ARTHUR SELZER, M D , AND PATRICIA McLEAN, B A
SAN FRANCISCO

With the introduction of the original prontosil (the hydrochloride of 4-sulfamido-2', 4'-diaminoazobenzene) by Domagk ¹ and the confirmation of the action of sulfanilamide and its derivatives by other observers,² a new era in chemotherapy was begun. The discovery of sulfanilamide as the effective principle in the prontosil molecule and the widespread use of this drug in treatment of infections other than those due to the hemolytic streptococcus quickly followed. A further impetus was given to progress in this renascent field in 1938 by the clinical introduction of sulfapyridine (2-[paraaminobenzenesulfonamido] pyridine) by Whitby,³ who demonstrated its striking efficacy in treatment not only of infections due to the pneumococcus but also of those due to the hemolytic streptococcus. These initial observations of Whitby, like those of Domagk, were quickly and amply confirmed in the last several years by numerous workers ⁴

From the Harold Brunn Institute for Cardiovascular Research, Mount Zion Hospital

1 Domagk, G. Ein Beitrag zur Chemotherapie der bakteriellen Infektionen, *Deutsche med Wchnschr* **61** 250, 1935

2 Levaditi, C, and Vaisman, A. Action curative et preventive du chlorhydrate de 4-sulfamido-2, 4-diamino-azobenzène dans l'infection streptococcique expérimentale, *Compt rend Acad d sc* **200** 1694, 1935. Colebrook, L, and Kenny, M. Treatment of Human Puerperal Infections and of Experimental Infections in Mice with Prontosil, *Lancet* **1** 1279, 1936. Buttle, G A H, Gray, W H, and Stephenson, D. Protection of Mice Against Streptococcal and Other Infections by *p*-Aminobenzenesulphonamide and Related Substances, *ibid* **1** 1286, 1936. Long, P H, and Bliss, E A. Use of *p*-Aminobenzene Sulphonamide (Sulfanilamide) or Its Derivatives in the Treatment of Infections Due to Beta Hemolytic Streptococci, Pneumococci and Meningococci, *South M J* **30** 479, 1937. Mellon, R R. New Approach to Therapeusis of Hemolytic Streptococcal Infections, *Proc Soc Exper Biol & Med* **34** 474, 1936

3 Whitby, L E H. Chemotherapy of Pneumococcal and Other Infections with 2-(*p*-Aminobenzenesulphonamido) Pyridine. *Lancet* **1**.1210, 1938

4 Evans, G M, and Gaisford, W F. Treatment of Pneumonia with 2-(*p*-Aminobenzenesulphonamido) Pyridine, *Lancet* **2** 14, 1938. Telling, M, and

(Footnote continued on next page)

Despite this rapid advance in the treatment of various infectious diseases, the fundamental mode of action of both of these drugs is still not completely understood. For there were those⁵ who expressed the belief that sulfanilamide, and by inference sulfapyridine, too, changes into some more powerful compound within the body, others⁶ stated the opinion that these drugs may act by the potentiation of tissue resistance to invasion by bacteria and thus act to combat effectively specific infections. But it would seem at the present writing that the majority of observers⁷ have concluded that the action of the drug is fundamentally exercised directly on the micro-organism and consists of the partial destruction or inhibition of the proliferation of the organism. Further, they suggested that in general the *in vivo* and the *in vitro* actions of these drugs are essentially similar.

Undoubtedly, as Long and Bliss pointed out in their excellent monograph,^{7a} many of the discrepancies present in the literature concerning the mode of action of these drugs were probably due to differences in environmental conditions present in the studies, for it has been shown that their action is a variable function which is dependent to a great degree on environmental factors, such as temperature control, the type of medium used, the presence or absence of peptone in the medium, the type and strain of organism used, the duration of the experiment and, finally, the size of the initial inoculum of bacteria which are being tested. Then, too, the inability of investigators to evaluate the *in vivo* action of sulfanilamide or sulfapyridine in the absence of any possible direct

Oliver, W. A. Case of Massive Pneumonia with Massive Collapse, Treated with 2-(*p*-Aminobenzenesulphonamido) Pyridine, *ibid* **1** 1391, 1938. Flippin, H., and Pepper, D. S. Use of 2-(*p*-Aminobenzenesulphonamido) Pyridine in the Treatment of Pneumonia, *Am J M Sc* **196** 509, 1938.

5 Levaditi, C., and Vaisman, A. La chimiotherapie antiendotoxique, *Ann Inst Pasteur* **61** 635, 1938. Mayer, R. L. Recherches sur le mecanisme de l'action antistreptococcique de l' amino-benzenesulfamide et de ses derives, *Bull Acad de med, Paris* **117** 727, 1937. Locke, A., Main, E. R., and Mellon, R. R. Anti-Catalase and the Mechanism of Sulfanilamide Action, *Science* **88** 620, 1938.

6 McKinney, R. A., and Mellon, R. R. Sulfanilamide and Macrophage Response to Hemolytic Streptococci in Mice, *Proc Soc Exper Biol & Med* **37** 333, 1937. Finklestone-Sayliss, H., Paine, C. G., and Patrick, L. B. Bacteriostatic Action of *p*-Aminobenzenesulphonamide upon Hemolytic Streptococci, *Lancet* **2** 792, 1937.

7 (a) Long, P. H., and Bliss, E. A. Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds, New York, The Macmillan Company, 1939. (b) Gay, F. P., and Clark, A. R. On the Mode of Action of Sulfanilamide in Experimental Empyema, *J Exper Med* **66** 535, 1937. (c) Levaditi, C. La chimiotherapie des infections microbiennes. Son mecanisme d'action, *Schweiz Ztschr f allg Path u Bakt* **1** 365, 1938. (d) MacMahon, B. J. Influence of Sulfanilamide on Infected Sinuses of Rabbits. Chemical and Microscopic Studies, *Arch Otolaryng* **28** 222 (Aug) 1938.

interference by the animal's own tissue has of course been partially responsible for the obscurity surrounding the mode of action of these drugs

Despite the vast amount of work that has been done in relation to the effect and mode of action of these two drugs on the hemolytic streptococcus, the pneumococcus and other organisms, relatively little work has been reported concerning their possible mode of action and their effect on *Streptococcus viridans* under controlled conditions, and the reports that are available are contradictory and rather vague. Thus, Long and Bliss⁸ reported that sulfanilamide in concentrations of $\frac{1}{10,000}$ markedly inhibited the growth of the alpha hemolytic streptococcus. However, Britton⁹ tested three strains of *Sti viridans* and found that two were unaffected by a concentration of sulfanilamide as high as $\frac{1}{500}$ and the third strain was inhibited in its growth only when the concentration of sulfanilamide was as high as $\frac{1}{1,000}$. Further, Maegraith and Vollum¹⁰ found that sulfanilamide and sulfapyridine acting in defibrinated blood previously deprived of leukocytes had no measurable effect on *Sti viridans*, but if these same experiments with blood were repeated in the presence of leukocytes it was found that a concentration of either drug as low as $\frac{1}{60,000}$ would effect bacteriostasis. The studies cited were all made *in vitro*, and there have been no *in vivo* experiments concerning the effect of these drugs on *Str viridans*, for, as Whitby¹¹ has pointed out, inability to produce an infection with this organism in the experimental animal has made it impossible to determine the *in vivo* efficacy of either sulfanilamide or sulfapyridine on *Sti viridans* under controlled conditions.

Likewise, there have also been few reports concerning the use of either drug in the treatment of the clinical entity subacute endocarditis caused by *Str viridans*, and, as previously noted with reference to the experimental observations, the results are conflicting. Thus, although there are scattered reports¹² of cures obtained in cases of subacute endocarditis after the administration of sulfanilamide, the majority of

8 Long, P. H., and Bliss, E. A. Para-Amino-Benzene-Sulfonamide and Its Derivatives, *J. A. M. A.* **108** 32 (Jan. 2) 1937.

9 Britton, C. J. C. The Effect of Sulphonamide Compounds on Certain Bacteria *in Vitro*, *Brit. J. Exper. Path.* **19** 140, 1938.

10 Maegraith, B. G., and Vollum, R. L. The Bacteriostatic Effects of Sulphonamide-P, Soluseptasine, and M & B 693, *Brit. M. J.* **2** 985, 1938.

11 Whitby, L. E. H. Chemotherapy of Bacterial Infections, *Lancet* **2** 1095, 1938.

12 Major, R. H., and Leger, L. H. Recovery from Subacute Infectious Endocarditis Following Prontosil Therapy, *J. A. M. A.* **111** 1919 (Nov. 19) 1938. Long and Bliss^{7a}

reports¹³ concerning the efficacy of sulfanilamide are extremely pessimistic. With the possible exception of the cases reported by Kelson and White,¹⁴ who treated their patients with sulfapyridine and heparin, no report could be found which indicated that sulfapyridine was of any real aid in the treatment of subacute endocarditis, but several reports¹⁵ have been published concerning its seeming inefficacy in the treatment of this disease.

Although it may be only of scientific interest to determine in infections caused by the hemolytic streptococcus or pneumococcus whether sulfanilamide and sulfapyridine act directly on the invading micro-organism or act to increase the tissue resistance against the invasion, it becomes of the utmost practical importance in the consideration of any chemotherapeutic approach to the disease subacute endocarditis to determine the exact mode of action of the drugs concerned. For this disease has been shown¹⁶ to be unlike the ordinary infection caused by a hemolytic streptococcus in that it is primarily a focus of growing, relatively avirulent streptococci in a fibrin-platelet mass which not only completely isolates the organisms contained within it from the living tissue of the body (circulating as well as fixed) but also may act to prevent them from coming into contact with any particular chemical substance which may be introduced into the blood stream. Accordingly, if sulfanilamide or sulfapyridine, or any other drug for that matter, is to be effective in the treatment of this disease, this drug must not only be able to destroy or markedly inhibit the growth of *Str. viridans* without the physical aid of living tissue but, just as important, also be able to penetrate the fibrin-platelet barrier, characteristic of this disease, in sufficient concentration to effect its results. Conversely, if a drug depends on the potentiation of living tissue resistance for its effective-

13 Klee, P. H., and Romer, H. *Prontosil bei Streptokokkenkrankungen*, Deutsche med. Wchnschr. **61** 253, 1940. Spink, W. W., and Crago, F. H. Evaluation of Sulfanilamide in the Treatment of Patients with Subacute Endocarditis, Arch. Int. Med. **64** 228 (Aug.) 1939. Sailer, S. Subacute Bacterial Endocarditis Treated with Sulfanilamide Resulting in Granulocytopenia and Death, Am. J. Clin. Path. **9** 269, 1939. Fuge, K. Die Behandlung der Puerperalsepsis mit Prontosil, Deutsche med. Wchnschr. **61** 1672, 1935.

14 Kelson, S. R., and White, P. D. New Method of Treatment of Subacute Bacterial Endocarditis, Using Sulfapyridine and Heparin in Combination, J. A. M. A. **113** 1700 (Nov. 4) 1939.

15 Ellis, G. R. Treatment of Subacute Bacterial Endocarditis with M & B 693, Lancet **2** 1521, 1938. Long and Bliss^{7a} Whitby¹¹

16 (a) Friedman, M., Katz, L. N., and Howell, K. Experimental Endocarditis Due to *Streptococcus Viridans*. Biologic Factors in Its Development, Arch. Int. Med. **61** 95 (Jan.) 1938. (b) Friedman, M. A Study of the Fibrin Factor in Relation to Subacute Endocarditis, J. Pharmacol. & Exper. Therap. **63**. 173, 1938.

ness or if it is unable to penetrate a physicochemical barrier in sufficient amount to eradicate or inhibit the growth of organisms protected by this barrier, it will probably be of no value in the treatment of an infection that is so routinely characterized by its isolation from living tissue and its physicochemical barriers to therapeutic accessibility

With a view to studying sulfanilamide and sulfapyridine and their properties in the light of the principles discussed, a series of experiments and observations were executed to determine (1) the degree of penetrability of both drugs through fibrin-platelet masses, (2) the *in vitro* effects of both drugs on three different strains of *Str viridans*, (3) the *in vivo* effects of both drugs on animals harboring these three strains of *Str viridans* but with the complete isolation of the microorganisms from the living tissue of the animal, (4) the effects of the prolonged administration of both drugs on the persistence of an infection artificially induced by *Str viridans* within an animal and, finally, (5) the actual results obtained with the administration of both of these drugs to patients suffering with subacute endocarditis due to *Str viridans*. From these experiments and observations, it was thought that a definitive evaluation of the effect of sulfanilamide and sulfapyridine in the treatment of subacute endocarditis could be made. Further, it was thought that the experiments allowed for the first time a direct comparison between the *in vitro* and the *in vivo* effects of the drugs without the final results being obscured by the complicating effects of interference by living tissue.

I PERMEABILITY OF FIBRIN MASSES TO SULFANILAMIDE AND SODIUM SULFAPYRIDINE

Method—For this study, an apparatus previously designed and described^{16b} was used which allowed the determination of the penetrability of a fibrin membrane by sulfanilamide and sulfapyridine. The mass itself was made by rotating a stirring rod in freshly drawn dogs' blood and then removing the fibrin-platelet membrane formed around the rod immersed in the blood. This membrane was cut to appropriate size and inserted between the two glass cylinders of the apparatus and was always tested for gross leaks at the beginning and at the end of any experiment. If no initial leak was present, sulfanilamide or sulfapyridine in varying concentrations was added to one cylinder (cylinder 1) and a physiologic solution of sodium chloride was added to the other (cylinder 2). At intervals, a small sample was removed from the cylinder originally containing only physiologic solution of sodium chloride and was tested for sulfanilamide or sulfapyridine, whichever was being used. The capacity of each cylinder was 3 cc, and the diameter of the fibrin barrier was 5 mm.

Results—Inspection of table 1 shows clearly that the rate of diffusion of either drug through a fibrin membrane is not constant, but in no experiment was there even 50 per cent diffusion of either drug through the thinnest of membranes in twenty-four hours. When it is considered that a vegetation is many millimeters in thickness and that rarely is the sulfanilamide or sulfapyridine at a constant level

of 10 to 20 mg per hundred cubic centimeters of blood over many days, it can easily be seen that it is questionable whether an effective amount of either drug could ever reach the interior of a vegetation and render it sterile. This might well explain the frequent clinical observation that the disease apparently progresses despite a negative blood culture.

II EFFECT OF SULFAPYRIDINE ON THE GROWTH OF STR VIRIDANS

Method—Since our primary object was to study the effect of parenterally administered sulfanilamide and sulfapyridine acting without the aid of any possible influence of living tissue, a means had to be effected for introducing the streptococci in the body of the animal, yet isolating them from any actual physical contact

TABLE 1—*Diffusion of Sulfanilamide and Sodium Sulfapyridine Through a Fibrin Mass*

Initial Concentration of Drug in Cylinder, Mg per 100 Cc	Thickness of Fibrin Membrane, Mm	Concentration of Drug in Cylinder 2, Mg per 100 Cc			
		1 Day	3 Days	6 Days	9 Days
		Sulfanilamide			
500	10	320			
500	10	260			
100	10	65			
100	10	190			
100	10	100	230		
20	10	30	100		
20	10	40	100		
10	10	10	30		
10	20	05	05		
Sodium Sulfapyridine					
50	30	05	70		
20	15		05	20	60
20	60		05	30	60

with living tissue. For this purpose, porcelain filters (two to three) of 10 cc capacity were devised, the open end of which could be sealed with a rubber cap which was then dipped in paraffin, the filters thus being made completely leak proof. Also, because the *in vivo* action of sulfanilamide was to be compared with its *in vitro* action under the same environmental conditions, glass containers open at one end were fitted with rubber caps and sealed completely with paraffin.

A preliminary series of experiments was performed with these porcelain filter capsules in order to determine the amount of parenterally given sodium sulfapyridine which would enter the interior of the capsule and the time factor which was involved. It was found that if the porcelain capsules were inserted into the peritoneal cavities of rabbits and 0.5 Gm of sodium sulfapyridine was given intravenously every two hours to these rabbits, at the end of six hours the average concentration of sodium sulfapyridine in a capsule was 4.9 mg per hundred cubic centimeters (eight experiments). It was found that if the capsules were initially filled with a solution containing a concentration of sodium sulfapyridine of 5 mg per hundred cubic centimeters and then placed in the abdomens of rabbits who later received no sulfapyridine, at the end of six hours the concentration had fallen

to 38 mg per hundred cubic centimeters (four experiments) Thus, it was found that a transfer of sulfapyridine could occur in either direction, that is, either from the body fluids into the capsule or from the capsule to the body fluids

Three strains of organisms identified as *Str viridans*¹⁷ were used in these experiments, two of them were isolated from patients who were suffering from subacute endocarditis and the course of whose illness is reported later in this article The procedure consisted of obtaining 1 cc of a twenty-four hour dextrose broth culture, making a $\frac{1}{100}$ dilution and then adding 1 cc. of the dilution to 100 cc of a dog serum-dextrose broth mixture (50 per cent of each) Three different studies were made on each strain, with the exception of strain H In general six capsules were filled completely with the serum-*Str viridans*-dextrose broth mixture Two glass containers were also filled with the same mixture plus enough sodium sulfapyridine to give a concentration of 5 mg per hundred cubic centimeters Then 4 rabbits were anesthetized, their abdomens were opened, and 3 of these rabbits received two filter capsules each and the fourth rabbit the two glass containers Two of the 3 rabbits receiving filter capsules then received 0.5 Gm of sodium sulfapyridine intravenously every two hours until 3 Gm of the drug had been given at the end of ten hours Then injections were omitted for eight hours and again resumed every two hours, until at the end of twenty-four hours each animal had thus received a total of 4.0 to 4.5 Gm of sodium sulfapyridine The remaining rabbit receiving the filter capsules was given no sulfapyridine and these capsules served as a control Likewise, the animal containing the two glass tubes received no sodium sulfapyridine except that placed initially in the tube Rectal temperatures were uniformly taken about eight hours after the insertion of the capsules At the end of twenty-four hours the animals' abdomens were incised, the capsules were removed and opened, the fluid was removed under aseptic conditions and bacterial counts, determination of the sulfapyridine content and direct inoculation of blood agar were made In the second series reported under subsection B, the same procedure was carried out except that the mixture placed in four of these filter capsules contained 5 mg per hundred cubic centimeters of sodium sulfapyridine, the remaining two filter capsules contained no sodium sulfapyridine and were inserted into a rabbit who also received no sulfapyridine, thus they served as the control In the third series, reported under subsection C the same procedure was followed except that four of the filter capsules contained 10 mg per hundred cubic centimeters of sodium sulfapyridine, the remaining two filter capsules still contained no sulfapyridine and served as the control

Results—A Effect of Sulfapyridine (parenterally administered) on *Str Viridans* As can readily be seen from table 2, although all the filter capsules placed in the animals receiving sodium sulfapyridine intravenously had a significant concentration of sulfapyridine within them at the end of twenty-four hours there was relatively little effect of this administered sodium sulfapyridine on the growth of any of the three strains when compared with the growth within the control filter capsules contained in the abdomens of rabbits receiving no sulfapyridine The marked bactericidal action of the sodium sulfapyridine acting in the glass tubes, which was in reality an *in vitro* experiment, appears at first paradoxical in the light of various investigations which have demonstrated that the *in vivo* action of sulfapyridine was as strong as, or perhaps stronger than its *in vitro* action However, as has already been mentioned, at least six hours must elapse before

17 Dr Lowell Rantz, of Stanford University School of Medicine determined the identity of the three strains used in these experiments

TABLE 2—Effect of Parenteral Administration of Sodium Sulfa-pyridine on *St. Typhimurium*

Rabbit	Type of Container Introduced Within Rabbit's Abdomen *	Initial Sodium Sulfa-pyridine in Container, Mg per 100 Cc	Total Parenteral Administration of Sodium Sulfa-pyridine, Gm	Sulfa-pyridine in Container After 24 Hours, Mg per 100 Cc	Initial Number of Streptococci Added to Container	Number of Streptococci in Container After 24 Hours	Temperature of Rabbit 8 Hours After Operation (C)	Growth of Container Fluid on Blood Agar	Duration of Experiment, Hours
Strain H									
1	Filter capsules { Ia { IIa	0	45	60	12 × 10 ⁸	1.0 × 10 ¹¹	40.0	+++	24
		0	45	58	12 × 10 ⁸	2.8 × 10 ¹¹	40.0	+++	24
2	Filter capsules { Ib { IIb	0	45	72	12 × 10 ⁸	6.0 × 10 ¹⁰	39.8	+++	24
		0	45	15	12 × 10 ⁸	1.7 × 10 ¹¹	39.8	+++	24
3	Glass capsules { Ic { IIc	5	0	50	12 × 10 ⁸	<1 × 10 ⁵ †	40.0	+	24
		5	0	46	12 × 10 ⁸	<1 × 10 ⁵ †	40.0	+	24
4	Filter capsules { Id (control) { IID (control)	0	0	0	12 × 10 ⁸	3 × 10 ¹¹	39.6	+++	24
		0	0	0	12 × 10 ⁸	1.5 × 10 ¹¹	39.6	+++	24
Strain R									
1	Filter capsules { Ia { IIa	0	45	45	1.5 × 10 ⁸	3.2 × 10 ¹⁰	39.2	+++	24
		0	45	42	1.5 × 10 ⁸	3.5 × 10 ¹⁰	39.2	+++	24
2	Filter capsules { Ib { IIb	0	45	38	1.5 × 10 ⁸	1.2 × 10 ¹¹	39.6	+++	24
		0	45	50	1.5 × 10 ⁸	2.0 × 10 ¹¹	39.6	+++	24
3	Glass capsules { Ic { IIc	5	0	48	1.5 × 10 ⁸	<10 × 10 ³ †	39.0	+	24
		5	0	48	1.5 × 10 ⁸	<10 × 10 ³ †	39.0	+	24
4	Filter capsules { Id (control) { IID (control)	0	0	0	1.5 × 10 ⁸	1.2 × 10 ¹¹	39.1	+++	24
		0	0	0	1.5 × 10 ⁸	2.5 × 10 ¹¹	39.1	+++	24
Strain S									
1	Filter capsules { Ia { IIa	0	15	42	1.5 × 10 ⁸	8.8 × 10 ¹⁰	39.8	+++	24
		0	15	50	1.5 × 10 ⁸	1.0 × 10 ¹⁰	39.8	+++	24
2	Filter capsules { Ib { IIb	0	45	35	1.5 × 10 ⁸	1.2 × 10 ¹¹	39.2	+++	24
		0	45	72	1.5 × 10 ⁸	1.2 × 10 ¹¹	39.2	+++	24
3	Glass capsules { Ic { IIc	5	0	48	1.5 × 10 ⁸	<10 × 10 ⁴ †	39.0	0	24
		5	0	49	1.5 × 10 ⁸	<10 × 10 ⁴ †	39.0	0	24
4	Filter capsules { Id (control) { IID (control)	0	0	0	1.5 × 10 ⁸	5.1 × 10 ¹¹	39.6	+++	24
		0	0	0	1.5 × 10 ⁸	3.2 × 10 ¹¹	39.6	+++	24

* As indicated in this table and in tables 3, 4 and 5, two capsules were introduced into each rabbit.

† Dilutions for counting were begun at this level.

the parenterally administered sulfapyridine enters the filter capsule in sufficient quantity to effect a significant concentration, so that during this lag period of six hours the growth of the organism may have easily taken place. Accordingly, it was decided to introduce into the filter capsules to be placed in sulfapyridine-treated animals enough sulfapyridine from the very beginning to effect a significant concentration during the first six hours and until the parenterally administered sulfapyridine entered in sufficient concentration.

B Effect of Parenterally Administered Sulfapyridine on Str Viridans When Sulfapyridine Was Initially Introduced Within the Filter and Glass Capsules (concentration of 5 mg per hundred cubic centimeters)

As can be seen in table 3, there was in all filter capsules in treated rabbits, regardless of the strain, a marked reduction in bacterial growth as compared to that in the control filter capsules inserted into untreated rabbits. Indeed, as table 3 indicates, in three of the filter capsules containing streptococci of the strain R variety there was complete sterilization, and in all filter capsules placed in treated animals there was not only bacteriostasis but actually partial sterilization, since the total number of bacteria present after twenty-four hours was less than the number added. It is of interest to note that in no strain was the *in vivo* action of parenterally administered sulfapyridine any more effective than the *in vitro* action of the sulfapyridine in the glass containers. It would seem, therefore, that the *in vivo* action of sulfapyridine on Str viridans differs in no respect from its *in vitro* action when living tissue is not in actual contact with the organism. This last factor may be of importance in the attack by these drugs on other organisms, but, as already mentioned, in the vegetative endocarditis caused by Str viridans there is no living tissue in actual contact with the organism.

C Effect of Parenterally Administered Sodium Sulfapyridine on Str Viridans When Sulfapyridine Was Initially Introduced Within the Filter and Glass Capsule (concentration of 10 mg per hundred cubic centimeters)

As table 3 indicates, the same bactericidal effect was observed on the two strains tested as was previously found when the initial sodium sulfapyridine concentration was 5 mg per hundred cubic centimeters. In this group, too, it will be observed that the *in vivo* action of sodium sulfapyridine was no more effective than that observed within the glass containers. But it is important to point out that whether sodium sulfapyridine was acting in the glass container or in the filter capsule, having wandered from the blood stream, its action was potent and decidedly effective under these conditions and appeared adequate in itself.

III EFFECT OF SULFANILAMIDE ON THE GROWTH OF STR VIRIDANS

Since the action of sodium sulfapyridine was found to be so remarkably effective on the growth of Str viridans if the inoculums were small and if the sulfapyridine was administered at once, it was considered advisable to test the action of sulfanilamide on the same three strains of Str viridans in the same manner.

Methods—Exactly the same technic was used in this group of experiments as was used in the experiments with sulfapyridine, except that sulfanilamide instead of sodium sulfapyridine was initially introduced into the filter capsules and glass capsules placed in animals treated with sulfanilamide. Two sets of experiments were carried out, the first with an initial concentration of sulfanilamide of 5 mg per hundred cubic centimeters in the appropriate filter and glass capsules, the

TABLE 3—Effect of the Parenteral Administration of Sulfapyridine on the Growth of *St. Viridans* with Introduction of Sulfapyridine into Capsules before Peritoneal Implantation

Rabbit	Type of Container Introduced	Initial Sodium Sulfapyridine in Container, Mg per 100 Cc	Total Parenteral Administration of Sodium Sulfapyridine, Gm	Sulfapyridine in Container After 24 Hours, Mg per 100 Cc	Initial Number of Streptococci Added to Container	Number of Streptococci in Container After 24 Hours	Temperature of Rabbit 8 Hours After Operation (C)	Growth of Container Fluid on Blood Agar	Duration of Experiment Hours
Strain H									
1	Filter capsules { Ia	5	4.0	4.0	2.0×10^7	1.4×10	39.1	++	21
	{ Iia	5	1.0	5.0	2.0×10^7	9×10^4	39.1	+	21
2	Filter capsules { Ib	5	1.0	4.0	2.0×10^7	1.1×10^5	39.0	++	21
	{ Iib	5	1.0		2.0×10^7		39.0	—	21
3	Glass capsules { Ic	5	0	5.0	2.0×10^7	1.1×10^5	39.6	++	21
	{ Iic	5	0	5.0	2.0×10^7	2.1×10^7	39.6	++	21
4	Filter capsules { Id	10	4.0	11.0	2.0×10^7	$<1 \times 10^3$ *	39.0	+	21
	{ Iid	10	1.0	7.6	2.0×10^7	1×10^3	39.0	++	21
5	Filter capsules { Ie	10	1.0	5.0	2.0×10^7	8×10^4	40.2	++	21
	{ Iie	10	1.0	5.0	2.0×10^7	4×10^4	40.2	+	21
6	Glass capsules { If	10	0	10.0	2.0×10^7	2×10^5	39.6	++	21
	{ Iif	10	0	10.0	2.0×10^7	1×10^7	31.6	++	21
7*	Filter capsules { Ig (control)	0	0	0	2.0×10^7	1.3×10^{11}	39.1	++++	21
	{ Iig (control)	0	0	0	2.0×10^7	4.2×10^{11}	39.1	++++	21
Strain R									
8	Filter capsules { Ia	5	1.0	10.1	1.5×10^8	$<1 \times 10^5$ *	39.0	+	21
	{ Iia	5	1.0	11.0	1.5×10^8	$<1 \times 10^5$ *	39.0	0	21
9	Filter capsules { Ib	5	1.0	11.2	1.5×10^8	$<1 \times 10^7$ *	39.2	0	21
	{ Iib	5	1.0	10.0	1.5×10^8	$<1 \times 10^7$ *	39.2	0	21
10	Glass capsules { Ic	5	0	5.0	1.5×10^8	$<1 \times 10^5$ *	39.0	0	21
	{ Iic	5	0	5.0	1.5×10^8	$<1 \times 10^5$ *	39.0	0	21
11	Filter capsules { Id	10	4.5	12.0	1.5×10^8	$<1 \times 10^3$ *	40.2	+	21
	{ Iid	10	1.5	15.6	1.5×10^8	$<1 \times 10^3$ *	40.2	+	21
12	Filter capsules { Ie	10	1.5	14.2	1.5×10^8	$<1 \times 10^3$ *	39.6	+	21
	{ Iie	10	4.5	13.8	1.5×10^8	$<1 \times 10^3$ *	39.6	+	21
13	Glass capsules { If	10	0	9.0	1.5×10^8	$<1 \times 10^3$ *	39.2	0	21
	{ Iif	10	0	10.2	1.5×10^8	$<1 \times 10^3$ *	39.2	+	21
14	Filter capsules { Ig (control)	0	0	0	1.5×10^8	6.0×10^{11}	39.0	++++	21
	{ Iig (control)	0	0	0	1.5×10^8	1.7×10^{11}	39.0	++++	21
Strain S									
15	Filter capsules { Ia	5	4.0	5.0	1.1×10^8	1.3×10^5	40.5	++	21
	{ Iia	5	1.0	5.1	1.1×10^8	1.5×10^5	40.5	++	21
16	Filter capsules { Ib	5	4.0	6.5	1.1×10^8	4.0×10^4	39.0	+	21
	{ Iib	5	1.0	7.5	1.1×10^8	1.0×10^5	39.0	+	21
17	Glass capsules { Ic	5	0	5.0	1.1×10^8	$<1.0 \times 10^3$ *	39.5	+	21
	{ Iic	5	0	5.0	1.1×10^8	$<1.0 \times 10^3$ *	39.5	+	21
18	Filter capsules { Id (control)	0	0	0	1.1×10^8	1.8×10^{11}	39.3	++++	21
	{ Iid (control)	0	0	0	1.1×10^8	2.5×10^{11}	39.3	++++	21

* Dilutions for counting were begun at this level

second with an initial concentration of sulfanilamide of 10 mg in similar capsules. All filter capsules placed in untreated rabbits of course contained no sulfanilamide and served as controls. The rabbits were placed on the same schedule of injections as the sodium sulfapyridine-treated animals, except that the injections were given both intravenously and subcutaneously—approximately 10 cc of a 1 per cent solution of sulfanilamide intravenously and 50 to 80 cc of a 1 per cent solution of sulfanilamide subcutaneously at each injection. In some animals, this tremendous dose had to be reduced, as can be seen by inspection of table 4. As in the experiments with sodium sulfapyridine, the capsules were removed after twenty-four hours and studied in the same fashion as described before.

Results—A Effect of Parenterally Administered Sulfanilamide on the Str Viridans When Sulfanilamide Was Initially Introduced Within the Filter and Glass Capsules (concentration of 5 mg per hundred cubic centimeters)

Inspection of table 4 indicates that the action of sulfanilamide was not nearly as effective as the action of sodium sulfapyridine on the growth of the three strains tested, although there appeared to be definite bacteriostasis in strain R and even partial sterilization in strain S. However, the growth of strain H appeared to be little affected by either the in vitro or the in vivo action of the sulfanilamide. It will be noted that in some capsules the concentration of sulfanilamide after twenty-four hours was high, indicating the ready transfer of parenterally administered sulfanilamide from body fluids to the interior of the capsule.

B Effect of Parenterally Administered Sulfanilamide on Str Viridans When Sulfanilamide Was Initially Introduced Within the Filter and Glass Capsules (concentration of 10 mg per hundred cubic centimeters)

As shown again in table 4, the action of sulfanilamide on these three strains of streptococci was much less effective than that of sulfapyridine, but there seems to be no doubt that at this concentration there was definite bacteriostasis in all three strains and that there appeared to be a limited amount of sterilization in strains R and S. It should be observed that the in vivo action of sulfanilamide, acting alone, was no more effective than the in vitro action under the conditions of our experiments.

IV EFFECT OF SODIUM SULFAPYRIDINE ON A FIBRIN-PLATELET MASS INFECTED WITH STR VIRIDANS

The preceding experiments indicated that the parenteral administration of either sulfanilamide or sulfapyridine had a bacteriostatic effect on the three strains of Str viridans studied, although the action of sodium sulfapyridine appeared to be more effective, for there was not only marked bacteriostasis when it was given but partial and complete sterilization in some of the experiments with these three strains. However, it was seen that to effect bacteriostasis and sterilization by the administration of sodium sulfapyridine, and presumably also of sulfanilamide, it was necessary to reach an effective concentration of the drug within the capsule before the bacteria were too far advanced in their growth. To study this last point further, it was decided to introduce fibrin-infected masses, suspended in sterile dog's serum in the same type of filter capsules previously utilized, and after peritoneal implantation of these filter capsules to treat the rabbits daily with sodium sulfapyridine.

TABLE 4—Effect of the Parenteral Administration of Sulfanilamide on the Growth of *St. Viridans* with Introduction of Sulfanilamide into Capsules before Parenteral Implantation

Rabbit	Type of Container Introduced	Initial Sodium Sulfanilamide in Container, Mg per 100 Cc	Total Parenteral Administration of Sulfanilamide, Gm	Sulfanilamide in Container 24 Hours, Mg per 100 Cc	Initial Number of Streptococci Added to Container	Number of Streptococci in Container After 24 Hours	Temperature of Rabbit 8 Hours After Operation (C)	Growth of Container Fluid on Blood Agar	Duration of Experiment, Hours
Strain H									
1	Filter capsules { Ia {	5	18	15.0	10 × 10 ⁸	1.1 × 10 ¹¹	39.2	+++	24
	Filter capsules { Iia {	5	48	15.8	10 × 10 ⁸	2.8 × 10 ¹¹	39.2	+++	24
2	Filter capsules { Ib {	5	48	9.2	10 × 10 ⁸	7.5 × 10 ¹⁰	39.6	+++	24
	Filter capsules { Iib {	5	18	10.0	10 × 10 ⁸	1.0 × 10 ¹¹	39.6	+++	24
3	Glass containers { Ic {	5	0	5.0	10 × 10 ⁸	3.0 × 10 ¹¹	39.0	+++	24
	Glass containers { Iic {	5	0	5.0	10 × 10 ⁸	2.5 × 10 ¹¹	39.0	+++	24
4	Filter capsules { Id {	10	48	12.5	10 × 10 ⁸	4 × 10 ⁹	39.6	+++	24
	Filter capsules { Iid {	10	18	11.8	10 × 10 ⁸	1.2 × 10 ¹⁰	39.6	+++	24
5	Filter capsules { Ie {	10	3.0	8.5	10 × 10 ⁸	3.0 × 10 ⁹	40.0	+++	8
	Filter capsules { Iie {	10	3.0	7.7	10 × 10 ⁸	7.0 × 10 ⁹	40.0	+++	8
6	Glass containers { If {	10	0	10.0	10 × 10 ⁸	1.7 × 10 ¹⁰	39.6	+++	24
	Glass containers { Iif {	10	0	10.0	10 × 10 ⁸	2.0 × 10 ¹⁰	39.6	+++	24
7	Filter capsules { Ig (control) {	0	0	0	10 × 10 ⁸	9.0 × 10 ¹¹	39.2	+++	24
	Filter capsules { Iig (control) {	0	0	0	10 × 10 ⁸	7.5 × 10 ¹¹	39.2	+++	24
Strain R									
8	Filter capsules { Ia {	5	5.4	12.5	1.5 × 10 ⁸	4.5 × 10 ⁷	39.2	+++	24
	Filter capsules { Iia {	5	5.4	15.0	1.5 × 10 ⁸	3.0 × 10 ⁷	39.2	+++	24
9	Filter capsules { Ib {	5	5.4	10.2	1.5 × 10 ⁸	1.0 × 10 ⁸	39.4	+++	24
	Filter capsules { Iib {	5	5.4	12.1	1.5 × 10 ⁸	5.4 × 10 ⁷	39.4	+++	24
10	Glass containers { Ic {	5	0	5.0	1.5 × 10 ⁸	7.5 × 10 ⁷	39.0	+++	24
	Glass containers { Iic {	5	0	4.8	1.5 × 10 ⁸	6.0 × 10 ⁷	39.0	+++	24
11	Filter capsules { Id {	10	5.4	12.5	1.5 × 10 ⁸	1.0 × 10 ⁷	38.8	+++	24
	Filter capsules { Iid {	10	5.4	14.0	1.5 × 10 ⁸	2.0 × 10 ⁷	38.8	+++	24
12	Filter capsules { Ie {	10	5.4	15.2	1.5 × 10 ⁸	2.0 × 10 ⁷	39.0	+++	24
	Filter capsules { Iie {	10	5.4	14.0	1.0 × 10 ⁸	3.6 × 10 ⁷	39.0	+++	24
13	Glass containers { If {	10	0	10.0	1.5 × 10 ⁸	2.1 × 10 ⁷	39.2	+++	24
	Glass containers { Iif {	10	0	9.8	1.5 × 10 ⁸	2.8 × 10 ⁷	39.2	+++	24
14	Filter capsules { Ig (control) {	0	0	0	1.5 × 10 ⁸	8.7 × 10 ¹¹	39.0	+++	24
	Filter capsules { Iig (control) {	0	0	0	1.5 × 10 ⁸	9.4 × 10 ¹¹	39.0	+++	24
Strain S									
15	Filter capsules { Ia {	5	1.6	6.3	5.5 × 10 ⁷	7.5 × 10 ⁴		+++	8
	Filter capsules { Iia {	5	1.6	4.3	5.5 × 10 ⁷	6.5 × 10 ⁴		+++	8
16	Filter capsules { Ib {	5	3.2	3.3	5.5 × 10 ⁷	8.0 × 10 ⁴	39.2	+++	24
	Filter capsules { Iib {	5	3.2	4.0	5.5 × 10 ⁷	6.0 × 10 ⁴	39.2	+++	24
17	Glass containers { Ic {	5	0	5.3	5.5 × 10 ⁷	9.0 × 10 ⁴	39.8	+++	24
	Glass containers { Iic {	5	0	5.1	5.5 × 10 ⁷	7.5 × 10 ⁴	39.8	+++	24
18	Filter capsules { Id {	10	7.2	15.2	5.5 × 10 ⁷	4.0 × 10 ³	38.8	+++	24
	Filter capsules { Iid {	10	7.2	12.4	5.5 × 10 ⁷	8.0 × 10 ³	38.8	+++	24
19	Filter capsules { Ie {	10	7.2	16.0	5.5 × 10 ⁷	1.5 × 10 ⁴	39.4	+++	24
	Filter capsules { Iie {	10	7.2	12.0	5.5 × 10 ⁷	6.7 × 10 ³	39.4	+++	24
20	Glass containers { If {	10	0	9.0	5.5 × 10 ⁷	<5 × 10 ³ *	38.8	+++	24
	Glass containers { Iif {	10	0	9.0	5.5 × 10 ⁷	5.0 × 10 ³	38.8	+++	24
21	Filter capsules { Ig (control) {	0	0	0	5.5 × 10 ⁷	3.9 × 10 ¹¹	39.2	+++	24
	Filter capsules { Iig (control) {	0	0	0	5.5 × 10 ⁷	5.4 × 10 ¹¹	39.2	+++	24

* Dilutions for counting were begun at this level

and at intervals of days to open the abdomen and determine whether sterilization had occurred. In this manner, it was believed, a stimulation of the clinical disease process would be obtained, for this fibrin focus in the filter capsule would be isolated from living tissue, either fixed or circulating, and could be reached only by the fluids of the body, just as has been demonstrated is the condition in the vegetation of streptococcic origin situated on a heart valve.

TABLE 5—*Effect of Prolonged Parenteral Administration of Sulfanilamide and Sodium Sulfapyridine on the Persistence of a Focus of Infection by Str. Viridans*

Rabbit	Type of Container Introduced Within Rabbit	Strain of Organism	Daily Administration of Drug, Gm	Total Amount of Drug Given, Gm	Duration of Experiment, Days	Viable Str. Viridans Present in Capsule?	Final Concentration of Drug in Capsule, Mg per 100 Cc
Sulfanilamide							
1	Filter capsules { Ia	R	1.5	7.5	5	Yes	10.5
	{ IIa	R	1.5	7.5	5	Yes	9.0
2	Filter capsules { Ib	R	1.5	9.0	6	Yes	4.0
	{ IIb	R	1.5	9.0	6	Yes	5.0
3	Filter capsules { Ic	S	0.75	10.95	15	Yes	3.0
	{ IIc	S	0.75	10.95	15	Yes	6.0
Sulfapyridine							
4	Filter capsules { Ia	R	1.5	7.5	5	Yes	5.0
	{ IIa	R	1.5	7.5	5	Yes	6.0
5	Filter capsules { Ib	R	1.5	9.0	6	Yes	4.0
	{ IIb	R	1.5	9.0	6	Yes	5.0
6	Filter capsules { Ic	S	1.0	14.85	15	Yes	1.2
	{ IIc	S	1.0	14.85	15	Yes	3.0
Control							
7	Filter capsules { Ia	R	0	0	6	Yes	0
	{ IIa	R	0	0	6	Yes	0
8	Filter capsules { Ib	S	0	0	15	Yes	0
	{ IIb	S	0	0	15	Yes	0

Method—Into six of ten filter capsules were placed five fibrin-platelet masses, about 5 mm in diameter, which had been previously suspended for twenty-four hours in a dextrose broth culture of strain R organisms, then sterile dog's serum was added to fill the capsules completely. The remaining four filter capsules were treated in the same manner except that the fibrin masses introduced into their cavities were previously impregnated with strain S organisms.

After all capsules were capped with rubber and sealed with sterile paraffin, they were introduced into the peritoneal cavities of 5 rabbits, thus, 3 rabbits received two capsules each containing the fibrin-platelet masses impregnated with the strain R organisms, and 2 rabbits received two capsules each containing the fibrin-platelet masses impregnated with the strain S organisms. Then sodium sulfapyridine was administered parenterally (by intravenous and intraperitoneal injection) three times a day to 3 of these rabbits until the end of the experiment. The capsules in, the 2 remaining rabbits, which were not treated, one capsule containing strain

R and the other containing strain S organisms, were used as controls. At the end of the experiment, the rabbits were operated on again, the capsules were removed under aseptic conditions, blood agar plates were directly inoculated with their contents and a determination of the sodium sulfapyridine content was made.

Results—As table 5 clearly demonstrates, in none of the animals receiving sulfapyridine were the contents of the filter capsules sterile when examined at the end of the experiment, although in 1 animal the capsules remained in the peritoneal cavity for fifteen days and this animal received a total of 14.85 Gm of sodium sulfapyridine. It will be observed, too, that all capsules contained significant amounts of sodium sulfapyridine, indicating that there was a transfer of sodium sulfapyridine from the body fluids to the interior of the capsules. In the light of these observations, it must be concluded that the administration of relatively large amounts of sodium sulfapyridine will not sterilize a focus of infection caused by *Str. viridans* within the body of a rabbit if this focus is shielded from living tissue, even though sodium sulfapyridine therapy may be continued for as long as fifteen days.

V EFFECT OF SULFANILAMIDE ON A FIBRIN-PLATELET MASS INFECTED WITH *STR. VIRIDANS*

Although the relatively poor bacteriostatic effect of parenterally administered sulfanilamide on a small inoculum of *Str. viridans* not protected by fibrin offered almost no hope that prolonged administration of the drug would be more effective in the sterilization of a fibrin-platelet mass impregnated with *Str. viridans*, it was thought nevertheless advisable to determine actually the efficacy of this type of extended treatment.

Method—Exactly the same procedure as described under "Method" in section IV was carried out, except that sulfanilamide in 0.8 per cent solution was given parenterally (by intravenous and intraperitoneal injection).

Results—All capsules when examined (table 5), whether they had remained in the peritoneal cavity for five, six or fifteen days, revealed the persistence of *Str. viridans*. Also, determination of the capsular concentration of sulfanilamide demonstrated conclusively that sulfanilamide readily entered the capsule during the experiment. Again, as was found with the more potent sodium sulfapyridine, the effectiveness of parenterally administered sulfanilamide in sterilizing a focus of infection caused by *Str. viridans*, closely similar to an actual vegetation from a functional standpoint, was almost nil.

VI EFFECT OF SULFANILAMIDE AND SULFAPYRIDINE IN THE TREATMENT OF CLINICAL SUBACUTE ENDOCARDITIS

The results already described concerning the effectiveness of sulfapyridine and sulfanilamide on *Str. viridans* in relation to subacute endocarditis uniformly pointed to the fact that from an experimental viewpoint these drugs appear to be unable to eradicate a focus of streptococci growing in and protected by a fibrin-platelet mass. However, it would be foolhardy to suggest the complete elimination of the use of these drugs in the treatment of subacute endocarditis if there were some remote

possibility that they could effect clinical results, despite their seeming ineffectiveness on a focus of *Str viridans* under controlled laboratory conditions. Accordingly, a study of the cases of 12 patients treated with these drugs was made and the results analyzed. It is important

TABLE 6—*Data on Twelve Clinical Cases of Subacute Endocarditis Treated with Sulfapyridine and Sulfanilamide*

Case Number	Patient	Age, Years	Duration of Illness Before Treatment, Months	Dose per Day, Gm	Duration of Therapy, Days	Additional Therapy	Final Result
Sulfapyridine							
1	W R	60	2.5	5	105	Heparin, 35 days	Death*
2	N V	7½	2	4	6	Heparin, 21 days	Death
3	K J	20	5	3	10	Supportive measures	Death
4	G M	25	2	5.5	60	Supportive measures	Death
5	W N	23	2.5	4	15	Supportive measures	Death
6	A P	32	5	4	8	Supportive measures	Death*
Sulfanilamide							
7	S B	34	1.5	5	42	Heparin, 14 days	Death*
8	I G	61	0.5	2.5	21	Supportive measures	Death
9	H K	52	2	5	30	Supportive measures	Death*
10	S G	46	1	4 to 8	40	Cacodylate	Death
Sulfanilamide and Sulfapyridine							
11	G P	34	1.5	6 Gm of sulfanilamide for 6 days and 2 Gm of sulfapyridine for 8 days	14	Supportive measures	Death
12	C S	24	3.5	4 Gm of sulfanilamide for 4 days and 3 Gm of sulfapyridine for 5 days	9	Supportive measures	Death

* Autopsy was performed

to point out that these cases were not selected from one institution but were collected from five different hospitals and represent the last successive cases of this disease in three of these five institutions.

Each of the 12 patients studied exhibited a cardiac murmur or murmurs, splenomegaly, a minimum of two blood cultures positive for *Str viridans*, fever, progressive anemia and loss of weight. Ten of the patients also presented petechiae, 10 of them had red blood cells in their urine, and 5 had clinical evidences of embolus. In none of these

cases, with the exception of 1, was there any clinical doubt of the diagnosis, and in this 1 case the only doubt was whether rheumatic fever also was not present

As table 6 indicates, 6 of the 12 patients received sulfapyridine alone for a period varying from six to one hundred and five days, and in all 6 the results have been worthless. Two of these patients also received heparin in conjunction with the sulfapyridine. Patient W R (table 6) received 3 to 4 ampules of purified heparin a day for thirty-five days, together with 5 Gm of sulfapyridine over the same period. Patient N V (table 6) was given heparin with neoarsphenamine for twenty-one days, after a trial with sulfapyridine resulted in no improvement. In both of these patients, despite the maintenance of a prolonged coagulation time (fifteen to thirty minutes) for a period of five and three weeks, respectively, there was no noticeable improvement and the blood cultures continued to be positive. In the 2 patients just mentioned, the occurrence of a thrombus in the vein just beyond the needle through which the heparin was passing into the vein led us to believe that thrombus deposits may have continued on the vegetation despite the intensive heparin therapy.

Those 4 patients who received sulfanilamide alone fared no better, as table 6 shows, even though the therapy was of fairly long duration, averaging thirty-one days. It is of interest to point out that the blood cultures of these 4 patients continued positive for *Str viridans*, even those of S B, who also received heparin for fourteen days.

The 2 patients who received sulfanilamide and later sulfapyridine also died, although it is obvious that in neither case was the therapy extensive either in quantity of drugs given or in duration.

Thus, of these 12 patients, all have died. It would seem, then, that the effect of either of these drugs on *Str viridans* present in a cardiac vegetation is no more effective than that observed on the same organism under controlled experimental conditions.

COMMENT

The inability of either sulfanilamide or sulfapyridine to penetrate easily a fibrin-platelet mass containing *Str viridans* is of course discouraging, for these two drugs are ordinarily considered to be fairly diffusible and if they can penetrate the mass but slowly, it would seem that the chances for any new chemical substance to penetrate more readily will also be slight. Again, it must be emphasized that any drug used in the treatment of subacute endocarditis must be able to penetrate a fibrin-platelet mass if it is to be effective.

The production of a focus of protected growth of *Str viridans* in the abdomen of the rabbit with the concomitant parenteral administration

of sulfapyridine or sulfanilamide to the same animal gave interesting results. They indicated clearly that both of these drugs were no more effective against *Str. viridans* in vivo than they were in vitro but if the inoculum was small and if its growth had not been allowed to progress too far, the effectiveness of either drug, in particular that of sulfapyridine, was so marked that it was unnecessary to suppose that living tissue would have aided further in the destruction of the organism. It may well be that the powerful effect of these drugs when given parenterally to animals infected with the hemolytic streptococcus, as contrasted with their possible equivocal action on the same organism in the test tube, is due to the fact that the bacterial invasion in the body is relatively slight and the number of bacteria per unit of invaded tissue is small and far less than the average number of bacteria present in various test tube experiments concerned with the determination of the germicidal activity of these drugs.

Despite the remarkable effectiveness of sulfapyridine and the lesser effect of sulfanilamide on *Str. viridans* when these drugs were placed in immediate contact with a small inoculum, it was found that if there was as little as six hours' delay in the contact between either of the drugs and the initial inoculum of *Str. viridans* the bactericidal action of either drug, despite the concentrations finally obtained, was nil. Then, too, the experimental production of a fibrin-platelet mass infected with this same organism but separated from living tissue by means of a porcelain filter capsule led to a persistence of infection despite the quantity and duration of administration of either drug. It was thought that this last procedure was a simulation of the disease process present in the patient suffering from subacute endocarditis.

Finally, a study was made of the cases of 12 patients with subacute endocarditis caused by *Str. viridans* who were treated with sulfanilamide or sulfapyridine or both, and in every case the effectiveness of these drugs was found to be negligible. Patients in 3 of these cases received intensive heparin therapy in conjunction with sulfapyridine or sulfanilamide, and the results were equally negative. Although one of us (M. F.) and his associates¹⁸ were the first to suggest and use heparin in the treatment of subacute endocarditis and although favorable results have been reported by Kelson and White,¹⁴ it is now believed by us that its action either alone or with sulfapyridine is of no real value in the treatment of this disease.

18 Friedman, M., Hamburger, W. W., and Katz, L. N. Use of Heparin in Subacute Bacterial Endocarditis. A Preliminary Report, *J. A. M. A.* **113** 1702 (Nov. 4) 1939.

SUMMARY

The permeability of a fibrin-platelet mass to sulfanilamide and sulfapyridine was studied and was found to be limited

The *in vivo* action of sulfanilamide and sulfapyridine on *Str viridans* was studied by means of a new technic, and the results were compared with those from the *in vitro* action of the drugs It was found that the *in vivo* and the *in vitro* activity of these two drugs were apparently identical

The production of a focus of infection by *Str viridans* in the rabbit functionally similar to the focus of infection found in the patient suffering with subacute endocarditis was accomplished, and it was found that the administration of either sulfanilamide or sulfapyridine did not result in the sterilization of this focus, despite a substantial duration of therapy

A series of 12 clinical cases of subacute endocarditis treated with sulfapyridine and sulfanilamide is reported The patients in 3 of these cases also received heparin therapy The effect of sulfanilamide or sulfapyridine was found to be negligible The concomitant use of heparin in the treatment of 2 patients receiving sulfapyridine and of 1 patient receiving sulfanilamide did not increase the effectiveness of either drug in combating the infection

The sodium sulfapyridine and sulfanilamide used in these experiments were given to us by the Abbott Laboratories, North Chicago

Drs W S Middleton and P F Clark, of the University of Wisconsin, gave aid and encouragement in the experimental and clinical phases of this study Drs L Briggs, B Kaufman and J M Rector, of San Francisco, and Dr L N Katz, of Chicago, allowed us the use of their clinical protocols for this study Miss M Hooper gave technical assistance in the execution of this problem

A CORRELATION OF THE VELOCITY OF BLOOD FLOW AND THE BASAL METABOLIC RATE

SAMUEL BAER, M D

Associate in Medicine, the Jewish Hospital

AND

HAROLD J ISARD, M D

Lieutenant, Medical Corps, United States Marines

PHILADELPHIA

It is more than a hundred years since Parry,¹ Graves² and Basedow³ first accurately described hyperthyroidism and called attention to some of the cardiovascular derangements present in this condition, but it was not until twenty-five years ago that clinical calorimetry began to be widely adopted as an aid in the diagnosis of exophthalmic goiter. Today the determination of the basal metabolic rate is the laboratory procedure most frequently used in the differential diagnosis of disorders of the thyroid gland.

Disturbances of the thyroid gland, however, are not the only conditions producing changes in the basal metabolic rate. The basal metabolic rate is elevated not only in hyperthyroidism, but also in leukemia, congestive heart failure, some cases of hypertension, fevers, polycythemia vera and various glandular disturbances. Furthermore, hypopituitarism and malnutrition as well as hypothyroidism may lower the basal metabolic rate. For these reasons attempts have been made to find procedures other than the determination of the basal metabolic rate that might be of help in the differential diagnosis of these disorders.

During the past decade increasing interest has also been manifested in the estimation of the velocity of blood flow. Blumgart and his asso-

From the wards and outpatient departments, Jewish Hospital

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* At the time this work was done Dr. Isard was an assistant in the Metabolic Department, the Jewish Hospital

1 Parry, C. H. Collections from the Medical Writings of the Late Caleb Hillier Parry, London, Underwood, 1825, vol. 1, p. 478

2 Graves, R. J. Newly Observed Affection of the Thyroid Gland in Females, London M. & S. J. 7 516, 1835

3 Basedow, C. A. Exophthalmos durch Hypertrophie des Zellgewebes in der Augenhöhle, Wchnschr. f. d. ges. Heilk. 6 197 and 220, 1840

ciates⁴ first described the method using radium C for measuring the speed of the circulating blood. They^{4c} demonstrated that myxedema and thyrotoxicosis were accompanied by changes in the rate of pulmonary blood flow. Later Tarr, Oppenheimer and Sager,⁵ determining the circulation time by the decholin method, also reported an increased velocity of blood flow in hyperthyroidism and a slowing in myxedema. Others⁶ have confirmed their work. However, some of the data we obtained in studying circulation times seemed contrary to previously published results. We decided, therefore, to reinvestigate the subject and determine what correlation, if any, existed between the basal metabolic rate and the velocity of blood flow.

METHOD

The studies were performed on patients in the wards and outpatient departments of the Jewish Hospital. All circulation times were measured by us, and over 90 per cent of the determinations of the basal metabolic rate were done by the same technician.

The subjects for the study (if ambulant) were put to bed and made to lie quietly for one-half to one hour. With the patient satisfactorily at ease, the basal metabolic rate was then determined by means of the Jones or Sanborn machine. The test was considered satisfactory only if smooth, regular graphs were obtained. During the same morning, under basal conditions, circulation times were determined.

The circulation time (arm to tongue) of calcium gluconate⁷ was determined as described by Goldberg^{6b} and then by Baer and Slipakoff.⁸ By means of an 18 gage needle and a 10 cc syringe containing 8 cc of a 20 per cent solution of calcium gluconate, 4 cc was injected into an antecubital vein. The intravenous injection of a 20 per cent solution of calcium gluconate causes a sudden sensation of heat in the tongue and pharynx, which rapidly spreads to the face, perineum and extremities. We modified Goldberg's procedure by using 40 cc rather than the originally suggested 25 cc for each test. The greater quantity

4 (a) Blumgart, H., and Yens, O. C. Studies on Velocity of Blood Flow, *J Clin Investigation* **4** 1, 1927. (b) Blumgart, H., and Weiss, S. Velocity of Blood Flow in Normal Individuals, *ibid* **4** 16, 1927. (c) Blumgart, H., Gargill, S., and Gilligan, D. R. Velocity of Blood Flow in Myxedema and Thyrotoxicosis, *ibid* **9** 91, 1930. (d) Blumgart, H. Velocity of Blood Flow in Health and Disease, *Medicine* **10** 1, 1931.

5 Tarr, L., Oppenheimer, B. S., and Sager, R. V. Circulation Time Determined by Use of Sodium Dehydrocholate, *Am Heart J* **8** 766, 1933.

6 (a) Macy, J. W., Claiborne, T. S., and Hurxthal, L. M. Circulation Time in Relation to Metabolism in Thyroid and Pituitary States (Decholin Method), *J Clin Investigation* **15** 37, 1936. (b) Goldberg, S. J. Use of Calcium Gluconate as a Circulation Time Test, *Am J M Sc* **192** 36, 1936. (c) Circulation Time as a Diagnostic Aid in Hyperthyroidism, *Ann Int Med* **11** 1818, 1939.

7 Calcium gluconate, in the form of calcium gluconogalactogluconate, in a 20 per cent solution, was supplied by the Sandoz Chemical Works, Inc., New York.

8 Baer, S., and Slipakoff, B. G. Measurement of Circulation Times and the Agents Used in Their Determination, *Am Heart J* **16** 29, 1938.

gave a more intense reaction. The injection was timed from the moment it was begun until the instant the sensation of heat was felt in the throat. Duplicate readings were usually made with the remainder of the 8 cc.

With the same needle in situ, the circulation time (arm to lung) of ether (Hitzig⁹) was determined. A mixture of 5 minims (0.3 cc) of ether and 5 minims of physiologic solution of sodium chloride was injected intravenously, the end point was the perception in the patient's breath of ether vapor, which was readily recognized by the observer and frequently caused the patient to cough or grimace.

All circulation rates were recorded in seconds and timed by a stop watch from the beginning of the injection to the instant the end point was recognized.

RESULTS

Circulation Time of Ether—The circulation time (arm to lung) of ether was obtained in 250 determinations on 218 patients. Some of these results are summarized in table 1. One of us (Dr. Baer) and an associate⁸ previously confirmed the observations by Hitzig⁹ and Oppenheimer and Hitzig¹⁰ that the normal circulation time of ether ranges

TABLE 1—*Circulation Time of Ether (Arm to Lung)*

	Normal Health	Hyper thyroidism	Spontaneous Hypo thyroidism	Postoperative Hypo thyroidism
Number of patients	157	18	6	3
Number of determinations	178	23	6	3
Average time	5.8 sec	4.6 sec	7.0 sec	6.5 sec

from 3.5 to 8.0 seconds, with an average of 5.5 seconds. Four of the 250 determinations were outside the normal range. (The data on normal patients have not been presented in their entirety, but merely summarized.) In another paper¹¹ we showed that, with rare exceptions, the circulation time of ether falls within normal limits unless incipient or definite failure of the right side of the heart is present. There is nothing to contradict this statement in our studies here. The circulation time of ether, therefore, has little, if any, value in the study of metabolic disorders.

Circulation Time of Calcium Gluconate—By means of the method using the calcium gluconate, 399 tests of circulation time were done on 187 patients. Goldberg^{6b} and Baer and Slipakoff⁸ showed that the

9 Hitzig, W. H. Use of Ether in Measuring Circulation Time from the Antecubital Veins to the Pulmonary Arteries, *Am Heart J* **10** 1080, 1935.

10 Oppenheimer, B. S., and Hitzig, W. H. Use of Circulatory Measurements in Evaluating Pulmonary and Cardiac Factors in Chronic Lung Disorders, *Am Heart J* **12** 257, 1936.

11 Baer, S., and Isard, H. J. Use of Ether Circulation Time in the Diagnosis of Right Heart Failure, *Am J M Sc* **200** 209, 1940.

normal arm to tongue time obtained with a 20 per cent solution of calcium gluconate ranges from 9 to 16 seconds, with an average of 12.5 to 12.7 seconds. Performing the test with 40 cc rather than the 25 cc originally suggested by Goldberg,^{6b} we found (table 2) in 227 trials that the average was 12.1 seconds, 10 of the 227 determinations were outside the normal range, and only 1 varied more than a second from the extremes of normal. Determinations of the metabolic rate were done in 119 instances on 110 normal patients. All but 19 were within the accepted normal range for the basal metabolic rate ($+15$ to -15 per cent). In no adult patient clinically considered normal were both the basal metabolic rate and the circulation time outside the normal range.

Twenty-four patients with a clinical diagnosis of active hyperthyroidism were examined. The results are recorded in table 3. In

TABLE 2—*Circulation Time of a 20 Per Cent Solution of Calcium Gluconate (Arm to Tongue)*

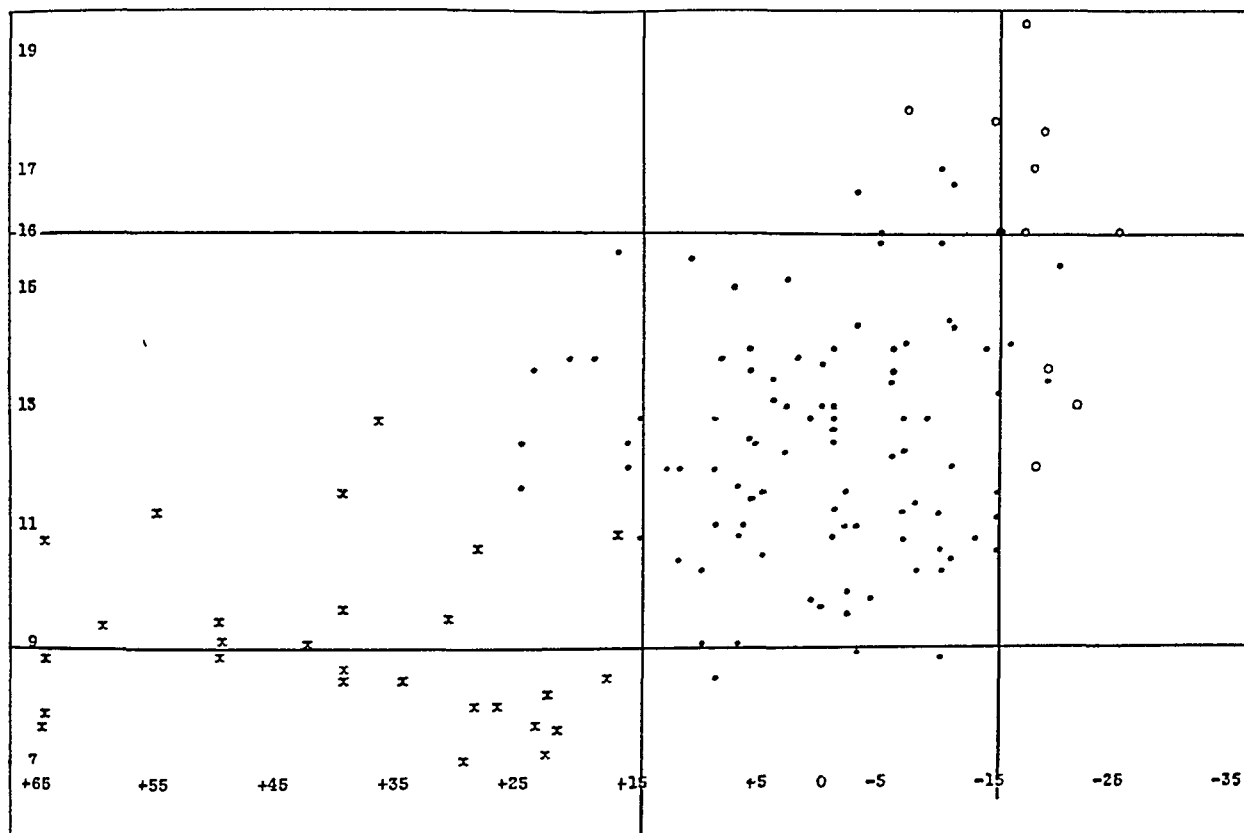
	Normal Health	Hyper thyroidism	Spontaneous Hypo thyroidism	Post operative Hypo thyroidism	Menopause with Hyper tension
Number of patients	110	24	6	3	18
Number of determinations	227	46	14	7	48
Average time	12.1 sec	8.9 sec	15.6 sec	17.6 sec	11.1 sec

this group the circulation time of calcium gluconate ranged from 7.0 to 13.2 seconds, with an average of 8.9 seconds. Tarr and his associates⁵ obtained 9.0 seconds, and Goldberg,^{6c} 8.8 seconds. Only 6 of the 46 determinations were above 10 seconds. Since a part of the basis for the diagnosis of hyperthyroidism was the basal metabolic rate, all but 1 of the patients had an elevated basal metabolic rate. This patient (case 280), with a basal metabolic rate of $+6$ per cent and a definite thyroid adenoma, had been taking compound solution of iodine U S P for months. Judged strictly, she could be eliminated from this group.

Table 4 lists the data on 9 patients with spontaneous and postoperative hypothyroidism. Of the 21 circulation times of calcium gluconate determined on these patients, 13 were prolonged to or beyond 16 seconds. The average circulation time for the patients with spontaneous hypothyroidism was 15.6 seconds and for those with postoperative hypothyroidism 17.6 seconds.

These results can be visualized more clearly on the graph, in which the circulation time is plotted against the basal metabolic rate. It would appear that though there is some overlapping of groups, an elevated

basal metabolic rate in hyperthyroidism is accompanied by a circulation time that is more rapid than normal or is in the low normal range. The patients with hypothyroidism, on the contrary, exhibit, in the majority of instances, a low basal metabolic rate and a circulation time above 13 seconds. In these patients there is some parallelism between the basal metabolic rate and the velocity of blood flow, as suggested by Blumgart, Gargill and Gilligan^{4c} and others¹³. When conditions simulating thyroid disorders were considered, however, this relationship did not hold.



A graphic presentation of the relation between the circulation time and the basal metabolic rate in normal persons (solid dots), patients with hyperthyroidism (x) and patients with hypothyroidism (hollow circles). The basal metabolic rate is plotted as abscissas and the circulation time in seconds as ordinates.

Table 5 lists the data on 6 patients with polyglandular dystrophy. It is apparent that there was no correlation whatsoever between the velocity of blood flow and the basal metabolic rate. In case 181 the patient exhibited prolonged circulation times despite a consistently elevated basal metabolic rate, and in case 61, a rapid circulation time.

Footnote 12 has been deleted.

13 (a) Webb, G., Sheinfeld, W., and Cohn, H. Importance in Surgery of Blood Circulation Time, *Ann Surg* **104** 460, 1936. (b) Fishberg, A. M. Heart Failure, Philadelphia, Lea & Febiger, 1937, pp. 527-539. (c) Tarr, Oppenheimer and Sager.⁵

TABLE 3—Data on Patients with Active Hyperthyroidism

Case Number	Sex	Age	Pulse Rate	Blood Pressure	Ether Time, Sec	Calcium Gluconate Time, Sec	Basal Metabolic Rate, per Cent
9	F	36	90	150/ 80	5 3	8 0 9 0	+63 +33 +65 +25 +53 +41
10	F	46	96	170/ 80	4 5	8 0 8 0	
12	F	33	88			7 4 8 2	+77 +100
29	F	62	89	175/100	5 0	9 2 10 0	+40
101	F	47	90	115/ 75	3 0	7 2 7 3	+30
114	F	28	86		5 4	12 8	+45 +30
176	F	63	90	170/ 60	5 0	9 0 9 0	+43 +44
157	F	35	90	110/ 75	4 8 5 5	10 0 9 0 7 8 9 0	+51 +49 +35
195	F	44	80	160/100	4 0	7 1 8 0	+22,
220	F	47	100		4 0	7 2 8 0	+73
215	F	27	80	120/ 80	5 0	8 1 9 4	+18
270	F	45	100	120/ 70	5 2	8 6 9 5	+70 +60 +43 +59
277	M	40	100	120/ 75	5 1	8 6 9 0	+77 +60 +43 +59
278	M	40	80	110/ 75		8 0	+29
231	F	41	95	112/ 70	4 0	8 0 9 0	+55 +46 +21
177	F	61	75	140/ 90	5 9	10 9	+17
280	F	57	85	170/ 90	4 5	10 0	+6
244	F	39	86	82/ 64	4 6	8 2 13 0	+29
252	M	46	150	130/ 60	5 2	10 4 11 2	+70
263	F	56	68	140/ 70		9 9 13 2	+46 +34
257	F	28	75		4 2	7 0 9 0	+27
274	M	26	90	140/ 80		9 1 9 8	+60
281	F	24	95	125/ 60		7 2 7 2	+19 +25
291	F	56	90	150/ 80		8 8 9 0	+45
Average					4 6	8 9	

TABLE 4—Data on Patients with Hypothyroidism

Case Number	Sex	Age	Weight, Pounds	Pulse Rate	Blood Pressure	Ether Time, Sec	Calcium Gluconate Time, Sec	Basal Metabolic Rate, per Cent
Spontaneous								
13	F	45	167¼	56	100/ 70	9 0	16 0	—25
21	F	50	151	66	110/ 80	8 0	12 0 13 0	—19 —18
50	F	46	114	52	120/ 18	7 2	16 0 12 6 13 2 16 0	—15 — 6 —17
81	F	38	157¼	44		4 4	18 0 21 2	—17
129	F	14	133½	64	110/ 75	7 0	14 0 20 0 20 0	—15
269	F	46	212	64	120/ 84	6 4	13 4 14 0 13 0	—21 —19 —11
Average						7 0	15 6	—21
Postoperative								
60	M	60	144	55	200/120	8 0 7 6	18 0 17 0 17 0	—18 — 2
11	F	24	140	84	130/ 90	4 0	18 0 18 0	— 7 —16
278	F	51	159	72	170/100		16 2	—19
Average						6 5	17 6	

TABLE 5—Data on Patients with Polyglandular Dystrophics

Case No	Sex	Age	Weight, Pounds	Pulse Rate	Blood Pressure	Ether Time, Sec	Calcium Gluconate Time, Sec	Basal Metabolic Rate, per Cent	Comment
181	F	40		95	215/115		17 8 18 0	+25 +50 +31	Hypertension and dyspituitarism
212	M	51	155¼	54	98/ 60	8 4 6 4	14 4 12 0 14 8 20 0	—17 — 1	Hypopituitarism
87	F	40	242	80	155/100	8 0	9 5 11 6	—30 +11	Adrenal cell rest tumors of both ovaries
61	F	19	133½	80	120/ 70	5 4 5 0	7 2 9 8 8 0 7 8 10 4	— 4 —20	Pituitary dysfunction
225	F	30	215	78	125/ 95	4 4	10 0	+17	Possible basophilic adenoma of pituitary
36	M	18	251	72		5 0 5 0 6 2	9 0 9 0 9 6 10 6 10 2 12 8	—19 —10 — 9	Dystrophic adiposo genitalis

and a low basal metabolic rate. Though these patients are few, we feel that they exhibit no relationship between the rapidity of blood flow and the metabolic rate.

TABLE 6—*Data on Patients with Menopausal Syndrome and Hypertension*

Case Number	Age	Weight, Pounds	Pulse Rate	Blood Pressure	Ether Time, Sec	Calcium Gluconate Time, Sec	Basal Metabolic Rate, per Cent
1	46	135	76	180/100	5 6 4 0 5 8	9 6 11 6 10 4 12 2 10 0 10 8	+22 — 1 +10
4	59	152½	60	148/100	6 0	12 2 12 4 12 0 12 0	+21 + 5
20	50	150½	64	155/ 95	7 2	11 4 11 2	—11
22	50	185	55	165/105	7 2	12 8 14 0 17 0	+25 — 8 — 5
26	42	165	80	178/100	5 2	9 4 10 4 10 4 8 8	+20 — 8 +19 — 3
34	49	166	82	195/ 95	5 0	8 8 9 0 7 8	— 8 +15
66	54	132	70	150/100	4 0	9 1 12 1	+ 6
92	40	217	60	150/ 90		8 4 11 0 9 2 9 8	—14 +22 +23 +25
105	48	147½	85	190/110	4 0	8 0 8 8	— 8
122	47	165	63	150/100	5 0	11 0 14 4	+ 5
139	50	169	66	140/100	7 4	10 4 11 4	+17
150	56	222	60	140/ 90	7 0	10 0 10 0	+ 9
163	42	195	72	130/ 90	4 8	10 4 11 4	+15
193	48	194½	62	180/ 90	8 0	11 2 11 4	+ 7
194	53	149	64	175/ 98	6 2	14 2 13 4	— 7
250	64	152	70	190/ 92	5 5	11 0 11 2	— 4
255	48	128¼	72	150/ 90	5 0	10 0 9 8	+ 4
272	37	131	88	130/ 90	6 2	9 8 10 0	+11
Average					5 7	11 1	

We further noticed during this study that a group of patients (table 6) with diverse clinical symptoms seemed to compose a definite class irrespective of the basal metabolic rates. These patients all had hypertension and were usually obese and in the menopausal period. King

and Sohval¹⁴ considered the value of the basal metabolic rate and the velocity of blood flow in the differential diagnosis of hyperthyroidism. Of their 87 cases, autonomic imbalance, menopausal syndrome, hypertension or nontoxic goiter was present in 70. In these borderline states neither the basal metabolic rate nor the circulation time was diagnostic,

TABLE 7—Data on Children

Case Number	Sex	Age	Weight, Pounds	Pulse Rate	Blood Pressure	Ether Time, Sec	Calcium Gluconate Time, Sec	Basal Metabolic Rate, per Cent
48	F	11	126	88		40 46	92 102 73 89	-20 -21 -14
253	M	9	69	75			80 78 80 101	-30 +19
15	F	13	145	70	110/70	70	115 110	-19
73	M	13	125	66	110/75	40	88 112	-8
185	F	11	72½	80		70	96 126	+11
202	M	10	100¼	72		42	72 96	+1
209	F	14	145½	62	115/75	50	92 98	-6
222	F	13	136	80		34	45 74 56	-16
224	F	16	133½	68	115/90	36	61 80	+6
227	F	16	168	68	106/88	14	84 82	+9
260	F	12		74		24	80 82	-1
52	F	15	168	76	100/60	58	110	-21
64	F	8	49	110	110/70	28	53 62	+12
70	F	9	95¼	80		40	72 60	+17 +20
160	F	10	77¼	80		40	104	+11
241	M	11	113¾	68		72	82 120	+2
Average						46	86	

the clinical judgment surpassed both laboratory studies in diagnostic accuracy. In the group of 18 patients we studied, circulation times ranged from 78 to 170 seconds, with an average of 111 seconds. Seven of the 50 measurements were outside the normal range of 90 to 160 seconds. Yet the basal metabolic rate varied from -14 to +25 per

14 King, F. H., and Sohval, A. R. Value of Basal Metabolic Rate, Velocity of Blood Flow and Creatinine Tolerance Test in Differential Diagnosis of Graves' Disease, *Ann Int Med* **13** 261, 1939.

cent, and in 9 of 30 estimations was above $+15$ per cent. In addition, repeated determinations of the basal metabolic rate showed a much greater variation than did the circulation times (cases 1, 4, 26, 34 and 92). The variations and overlapping in this group were such that we felt there was no definite relationship between the basal metabolic rate and the circulation time.

In table 7 are included data on 16 children on whom the basal metabolic rate and the velocity of blood flow were determined. Aver-buck and Friedman¹⁵ found the circulation time in children varied from 5.0 to 13.5 seconds, with an average of 8.6 seconds. The 35 determinations listed confirm their findings, our average also being 8.6 seconds. But it is seen that despite the consistently rapid circulation time in children, the basal metabolic rate varied from -21 to $+20$ per cent and bore no relationship whatsoever to the circulation time. Further study is necessary to determine whether the shorter pathway due to the physical measurement of the child is a prime factor in production of these rapid rates.

COMMENT

Blumgart and his associates^{4c} first pointed out that there was a relation between the velocity of blood flow, the pulse rate and the basal metabolic rate. Others¹⁶ confirmed their observations, reporting a strikingly increased velocity of blood flow in cases of hyperthyroidism. Our study bears this out, but we cannot agree with Blumgart and his associates^{4c} that the circulation time parallels the basal metabolic rate and that a given percentage of increase or decrease in the basal metabolic rate is accompanied by a far greater percentage of change in the velocity of blood flow. We did not, for example, observe consistently increased circulation times in cases of hypertension with an elevated basal metabolic rate. Macy and his co-workers^{6a} in studying the circulation rate in relation to metabolism, concluded there was no obvious circulatory change associated with hypometabolism which was not primarily thyroid in origin.

It would appear, then, that the basal metabolic rate itself is not the important factor influencing the velocity of blood flow in disturbances of the thyroid gland. Perhaps, as suggested by Fishberg,^{13b} it is the effect of the amount of circulating thyroxin on the metabolism of the heart muscle itself that plays a predominant role in the circulatory adjustments to hyperthyroidism and hypothyroidism.

15 Averbuck, S. H., and Friedman, W. Circulation Time in Normal Children, *Am J Dis Child* **49** 361 (Feb.) 1935.

16 Tarr, Oppenheimer and Sager⁵ Macy, Claiborne and Hurvathal^{6a} Goldberg^{6c} Webb, Sheinfeld and Cohn^{13a} Fishberg^{13b}

It must be realized that the circulation time may not always be diagnostic of hyperthyroidism, any more than is the basal metabolic rate. There is too much overlapping to make the measurement of the velocity of blood flow an absolutely diagnostic procedure. The final diagnosis in borderline cases may depend entirely on clinical judgment as suggested by King and Sohval¹⁴. They expressed the belief that the determination of the circulation time failed to give laboratory assistance in the differential diagnosis of exophthalmic goiter and the borderline states. We do believe, however, that it is of some definite value. Ninety per cent of the 46 determinations of the circulation time of calcium gluconate in patients with hyperthyroidism were 10 seconds or below. Of the normal group, only 22 per cent were 10 seconds or less, and of those patients exhibiting menopausal symptoms and hypertension, 39 per cent had circulation times of 10 seconds or below. An elevation of the basal metabolic rate above 20 per cent and a circulation time (arm to tongue) of calcium gluconate of 100 seconds or less in our opinion, are strongly suggestive of active hyperthyroidism.

SUMMARY AND CONCLUSIONS

The circulation time of ether was determined in 218 patients. The circulation time of ether is of no value in the study of metabolic disorders.

The circulation of calcium gluconate was measured in 227 determinations on 110 normal patients and averaged 12.1 seconds.

In patients with hyperthyroidism or hypothyroidism, the circulation time roughly paralleled the basal metabolic rate. The circulation time is rapid in hyperthyroidism and slowed in hypothyroidism.

There is no correlation between the circulation time of calcium gluconate and the basal metabolic rate in polyglandular dystrophies or menopausal syndromes with hypertension. Irrespective of the basal metabolic rate, the circulation time is rapid in children.

The determination of the velocity of blood flow may be of some help in the diagnosis of derangement of the thyroid gland.

Dr. Harold L. Goldburgh and Dr. Leon Jonas gave us permission to undertake this study and offered advice and criticism.

OSTEOGENESIS IMPERFECTA

ITS INCIDENCE AND MANIFESTATIONS IN SEVEN FAMILIES

F REGIS RIESENMAN, M D

AND

WALLACE M YATER, M D

WASHINGTON, D C

Thirty-two members of 7 white families having osteogenesis imperfecta have been found to reside in or near Washington, D C¹ In 5 of the families there is a definite hereditary tendency, while in the other 2 families with no such tendency the disease is represented in its isolated form The ascendants, descendants and collaterals of the various families were studied, and 91 cases of the disease were found in a total of 255 members Seven generations of 1 family, six generations of 2 families and five generations of another family were traced The origin of the condition in 1 of the family groups was in Ireland, in 1790, in 2 family groups, in Germany, 1 in 1735 and the other in 1770, and the remaining 4, in this country, 2 in Virginia, dating back to 1808 and 1896, and the other 2 in the District of Columbia

HISTORICAL DATA

Osteogenesis imperfecta, otherwise called fragilitas ossium, has been recognized for more than one hundred and fifty years and blue sclerotics for more than a hundred years, but as unrelated conditions The fragility factor was described by Ekman² in 1788, and the blue sclerotics were first recognized by Henzschel³ in 1831 The fact that the two conditions occur in the same families and frequently in the same patients and that they are inherited abnormalities was definitely established by Spurway in 1896 and by Eddowes in 1900⁴ The first definite descrip-

From the Department of Medicine, Georgetown University School of Medicine

1 The cases of only 8 of the 32 will be described in detail as illustrative material

2 Ekman, O J Descriptio et casus aliquot osteomalaciae, Upsala, J Edman, 1788

3 Henzschel, G Voraufge Notiz uber den Irisangel bei drei Geschwistern, Ztschr f d Ophth **1** 52, 1831

4 Spurway, J Hereditary Tendency to Fracture, Brit M J **2** 844, 1896
Eddowes, A Blue Sclerotics and Fragile Bones, *ibid* **2** 222, 1900, cited by
Rodger, T R Otosclerosis Associated with Blue Sclerotics and Fragilitas Ossium,
Proc Roy Soc Med **29** 1107 (July) 1936

tion of the disease was given by Lobstein cited by Levent⁵ in 1833 and his name is often given to this syndrome. In 1916, van der Hoeve and de Kleijn⁶ demonstrated before the Groningen Medical Society the association of deafness with abnormal coloration of the scleras and fragility of the bones. They subsequently described the syndrome which bears their names and which appears to be a particular and more complete form of the disease. The syndrome is not always complete; one or even two, of the symptoms in the triad may not be present. The most common member of the symptomatic triad is the ocular abnormality in which the scleras present "a porcelain or leaden-blue appearance which is very striking."⁷ The disease is transmitted as a dominant mendelian trait, the blue scleras being a more dominant factor than either the brittle bones or the deafness, so that affected persons may be expected to show blue sclerotics in from 90 to 100 per cent of cases and brittle bones with multiple fractures in 50 per cent. Deafness may be expected to occur in 25 per cent of those persons with blue scleras.⁸

CAUSATION

Although the exact cause of the disease is unknown, fundamentally the condition is due to the transmission of a defective gene or genes that characterize normal development of the mesenchyme, so that the problem is essentially one of a genealogic nature. It is the consensus that the disease is a hereditary inferiority of the mesenchyme.⁹ Perhaps the defective germ plasm may have resulted from a mutation of a gene or genes under the influence of certain factors in the external environment, so that the potentialities that they once possessed are no longer capable of free expression. The variation, being of a heritable nature, is consequently evidenced in the descendants. There is no definite proof that the endocrine system is involved or that the mineral metabolism is affected.¹⁰ In the majority of cases the metabolic processes are normal. One fact that seems to be quite consistent is that there is both a quantitative and a qualitative change in the osteoblasts while the osteoclasts are normal.¹¹

5 Levent, R. Syndrome de Lobstein. Syndrome de van der Hoeve, *Gaz. d. hôp.* **105** 1901 (Dec 21) 1932.

6 van der Hoeve, J., and de Kleijn, A. Blaue Sclera, Knochenbrüchigkeit und Schwerhörigkeit, *Arch. f. Ophth.* **95** 81, 1918.

7 Rodger, T. R. Otosclerosis Associated with Blue Sclerotics and Fragilitas Ossium, *Proc. Roy. Soc. Med.* **29** 1107 (July) 1936.

8 Fraser, I. Fragilitas Ossium Tarda, *Brit. J. Surg.* **22** 231 (Oct.) 1934.

9 Hilgenfeldt, O. Beitrag zum Krankheitsbilde der idiopathischen abnormen Knochenbrüchigkeit, *Deutsche Ztschr. f. Chir.* **238** 433, 1933.

10 Kraus, E. J. Osteogenesis imperfecta und endokrines System. *Virchow's Arch. f. path. Anat.* **274** 37, 1929.

11 Cinelli, A. A. Fragilitas Ossium with Otosclerosis and Blue Sclera. *Arch. Otolaryng.* **25** 309 (March) 1937.

FORMS OF THE DISEASE

The disease appears in three distinct forms ¹² (1) osteogenesis imperfecta congenita, (2) osteogenesis imperfecta tarda, or the infantile type, and (3) idiopathic osteopsathyrosis. The first two forms are congenital and include the presence of the blue scleras. The third form, or idiopathic osteopsathyrosis, shows the same manifestations as the congenital types with the absence of the blue discoloration of the scleras.

In osteogenesis imperfecta congenita numerous fractures are present at birth, and children with this form of the disease generally die in early infancy. If they survive they invariably remain chronic invalids for life. This is a rare form of the disease.

In osteogenesis imperfecta tarda the only manifestation at birth is the blue scleras. The fractures generally appear only when the child begins to walk. Occasionally the disease may not manifest itself until early adolescence or adult life, or may even remain latent throughout the person's life. This is the most common form of the disease.

Idiopathic osteopsathyrosis is to some extent a self-limited disease, it appears about the age of 3 and follows much the same course as the tarda form, but there are no blue scleras.

PATHOLOGIC FEATURES

The pathologic condition is practically limited to the mesenchyme, so that the bones, muscles, fasciae, ligaments and tendons show the greatest changes.

The bones of the extremities show the greatest degree of involvement. They are shorter, smaller and thinner than normal. There is an extreme degree of thinning of the cortex, a decrease in the cancellous and an increase in the medullary elements.⁸ The trabeculae are slender and delicate and widely separated by interstices filled with cellular connective or fibrous marrow. As a general rule, no cross trabeculae are present. The lamellae in the honeycomb lack the uniformity and regularity of normal bone. The architectural framework is greatly altered so that the lines of stress and strain are not ideally adapted to conform with the normal pressure relations.

Most striking roentgenographically is the extremely slender shaft which stands out in contrast to the expanded extremities (fig 1A). There is considerable disproportion in size of the epiphysis and the

¹² Sante, L. Osteogenesis Imperfecta. Principles of Roentgenological Interpretation, in Manual of Roentgenological Technique, Ann Arbor, Mich., Edwards Bros., Inc., 1940, chap 7, pp 106-108. Fairbank, H. A. Some General Diseases of the Skeleton, Brit J Surg **15** 122, 1928. Knaggs, R. L. Osteogenesis Imperfecta, *ibid* **11** 737 (April) 1924.

diaphysis with widening of the metaphysis¹³ Peculiar cross striations are usually present (fig 1 *B*) After cure the roentgenograms are normal Biopsy shows the extreme density and hardness of the bone It feels and cuts like marble

Fatty infiltration and phanerosis occur in the muscles, which become atrophic and hypotonic¹⁴ These changes occur both in striated and in

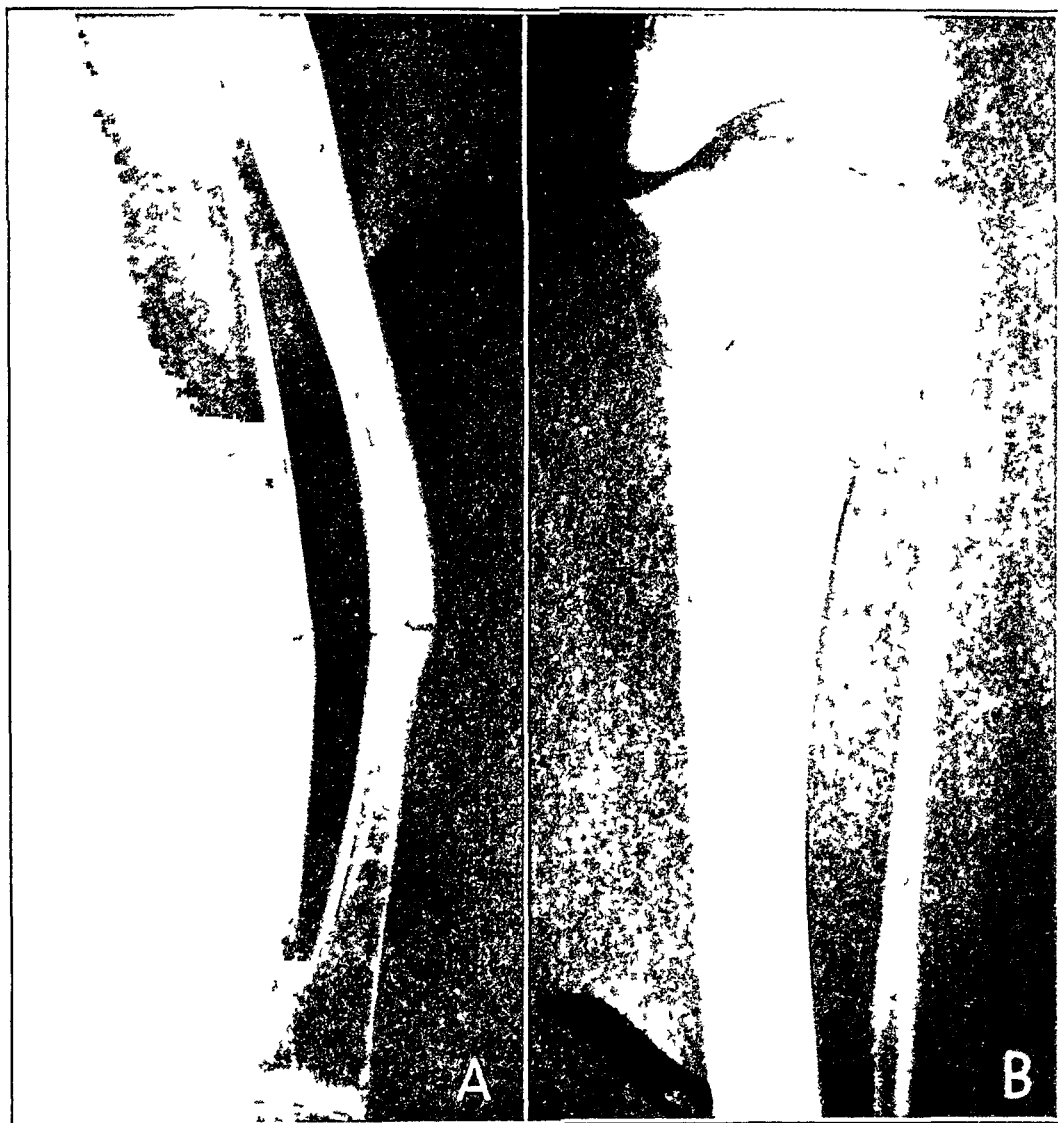


Fig 1—Osteogenesis imperfecta *A*, fracture of the middle of the tibia and fibula in a 9 year old girl (case 4) Note the pathognomonic cross striations in the upper end of the tibia and the narrow bones with a thin cortex *B*, fracture of the head of the tibia and fibula Note the cross striations in the upper third of the tibia

13 Dessoff, J Blue Sclerotics, Fragile Bones and Deafness, Arch Opnth 12 60 (July) 1934

14 Faber, M Sulla patogenesi dell osteogenesi imperfetta, Clin ostet 34 1 (Jan) 1932

smooth muscles The connective tissue likewise becomes altered, so that the ligaments, tendons and fasciae are involved¹⁵ The walls of vessels, particularly veins, become weak, and varicosities develop The supporting structures around the joints become lax, and abnormal motility, with frequent sprains and dislocations, results In the feet, the transverse arch, because of lack of support, gives way, and pes planus results

SYMPTOMATOLOGY

Osteogenesis imperfecta (hereditary mesenchymal hypoplasia) is characterized by various syndromes and presents the following clinical manifestations

A In the bones

- 1 Brittle bones with multiple fractures (50 to 65 per cent)¹⁶
- 2 Curvatures (saber deformity, scoliosis)
- 3 Bony prominences on the skull
- 4 Bone atrophy
 - (a) Primary (basic pathologic condition)
 - (b) Secondary (atrophy of disuse)
- 5 Small, short and thin bones

B In the joints

- 1 Enlargement of the joints
- 2 Laxity of the ligaments around the joints
- 3 Hypermotility of the joints
- 4 Double jointedness
- 5 Frequent sprains and dislocations
- 6 Pes planus

C In the eyes

- 1 Blue scleras (90 to 100 per cent)
- 2 Corneal astigmatism

D In the ears

- 1 Progressive otosclerosis (25 to 40 per cent)
 - (a) Tinnitus (70 per cent)
 - (b) Vertigo (10 per cent)

15 Shugrue, J J, Rockwood, R, and Anderson, E W Fragilitas Ossium and Deafness, Arch Int Med **39** 98 (Jan) 1927

16 Hills, R G, and McLanahan, S Brittle Bones and Blue Scleras in Five Generations, Arch Int Med **59** 41 (Jan) 1937

E In the muscles

- 1 Hypotonia (weakness and flabbiness)
- 2 Fatty infiltration and phanerosis
- 3 Atrophy
 - (a) Primary (basic pathologic condition)
 - (b) Secondary (atrophy of disuse)

F In the vessels

- 1 Connective tissue changes
- 2 Atrophy of the middle coat
- 3 Varicosities
- 4 Prominence of the superficial veins of the head

TREATMENT

Thus far there is no specific therapeutic agent for this disease. The use of thymus extract and estrogen has been reported to give results.¹⁷ This treatment, however, has usually not been instituted until the child has had one or several fractures. If there is any justification for the treatment at all, it would be a wise procedure to give thymus extract to the mother at about the fourth month of prenatal life, to maintain its use for the duration of pregnancy and if the child is born with the blue scleras to administer it to him during the first few years of life. By adopting such a course of treatment the thymus concentrate would be present during the more formative period of bone development and might predispose to a stronger skeletal structure. The rationale behind such a course of treatment is based on the theory that thymus extract exerts a strong influence on growth and development of bone in prenatal and early postnatal life.¹⁸ There is considerable experimental evidence in support of this concept.¹⁹

17 Ryan, W. J. Osteogenesis Imperfecta Tarda, *Ann Surg* **95** 771 (May) 1932, Osteogenesis Imperfecta, with a Suggestion for Treatment, *J Bone & Joint Surg* **14** 939 (Oct.) 1932. Stevenson, G. H., and Cuthbertson, O. P. Osteogenesis Imperfecta, *Lancet* **2** 782 (Oct. 10) 1931, cited by Wilson, P. D., and others. Forty-Sixth Report of Progress in Orthopedic Surgery, *Arch Surg* **24** 885 (May) 1932. Gorter, E. Treatment of Fragility of Bones with Thymus Extract, *Nederl tijdschr v geneesk* **73** 2022 (April 27) 1929. Kaplan, E. B. Multiple Fractures Associated with Blue Sclera, *J Bone & Joint Surg* **16** 625 (July) 1934.

18 (a) Gudernatsch, J. P. The Present Status of the Thymus Problem, *M Rec* **146** 101 (Aug. 4) 1937. (b) Rowntree, L. G. The Thymus Gland in Text. F. Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc. 1938, vol. 8, pp. 519-535. (c) Bartoli, O. Influenza del timo sulla guarigione delle fratture e sulla formazione del callo osseo, *Chir d org di movimento* **13** 168, 1928.

19 Enriques, P., and Robuschi, L. Rapporti funzionali tra ghiandole endocrine e frattura ossea, *Arch di fisiol* **24** 382 (July-Sept.) 1926, abstracted, *Endocrinology* **12** 98 (Jan-Feb.) 1928. Glassner, K., and Hass, J. Experimentelle Beeinflussung der Kallusbildung bei Knochenfrakturen, *Klin Wchnschr* **7** 1633 (Aug. 26) 1928, abstracted, *Endocrinology* **14** 379 (Sept.-Oct.) 1930. Gudernatsch,^{18a}

Orthopedic procedures will relieve the deformity and crippling to a large extent. Osteotomy and osteoclasis are the operations of choice, and union occurs after the operations.²⁰

The use of homologous bone grafts²¹ in patients with ununited fractures or with severe deformities of the bones of the lower extremities, and even in some who are unable to walk or stand, has met with great success. By such an operative procedure hopeless cripples are converted into happy and useful citizens. The application of properly fitting braces, when indicated, is also a valuable procedure.

Prophylactic measures in the way of precautions to guard against possible injury to the bones during infancy, childhood and early adolescence, including the application of braces to the lower extremities in cases of marked weakness of the bone structure, have an important place in the therapeutic regimen.

DIAGNOSIS

Little difficulty is encountered in the diagnosis of the congenital forms when the hereditary factor is present. The diagnostic triad is the blue scleras, the roentgenographic appearance of the bones and the history of the case.

The blue scleras are practically pathognomonic of the syndrome.¹⁶ Other indications associated with blue scleras are tuberculosis, severe anemia and poisoning by metals, particularly lead. At times a bluish tinge is noted in young infants and in some Negro children.

In cases of the congenital form in which the history is negative, the presence of the blue scleras together with the appearance of the roentgenograms will usually suffice for a diagnosis.

In cases of idiopathic osteopsathyrosis the diagnosis is based on the history, appearance of the roentgenograms and histologic studies of the bones if necessary.

Osteopathies that may clinically simulate the disease are rickets, tuberculous and syphilitic bone diseases, bone cysts and osteoporotic changes in the bones.

FAMILY GROUPS AND CASES

Because of the multiplicity of cases, time and space will not permit a detailed account of all, and the discussion of case reports will be confined to those cases that present the most interesting aspects of the disease, the other cases being simply mentioned in order to complete the family tree.

20 Colonna, P. C. Osteogenesis Imperfecta, *Am J Surg* **15** 336-340 (Feb) 1932.

21 Smith, A. DeF. Use of Homologous Bone Grafts in Cases of Osteogenesis Imperfecta, *Arch Surg* **34** 687-694 (April) 1937.

Family Group I—A study of this family group reveals that the condition originated in the family in Ireland in 1825 (fig 2). The disease was manifested at this time by the presence of deafness and a very small skeletal structure in 1 member. No definite information regarding the scleras in this person could be obtained. There were 7 siblings in the second generation, 1 of whom inherited the disease. Blue scleras, deafness and spinal curvature were the main manifestations of the disease in this person. In the third generation 5 of 9 siblings inherited the condition, and in the last generation 4 cases were found. Deafness was present in every member who inherited the condition.

CASE 1—J. O., a white man aged 48, single, was admitted to the hospital in March 1939 with the complaint of backache and swelling of the legs of two years' and six months' duration, respectively. He had had deep blue scleras from birth and a progressive type of deafness had made its appearance at the age of 7. The rest of the history was essentially irrelevant. With the exception of the deafness every abnormality was found on general inspection. The patient was short and

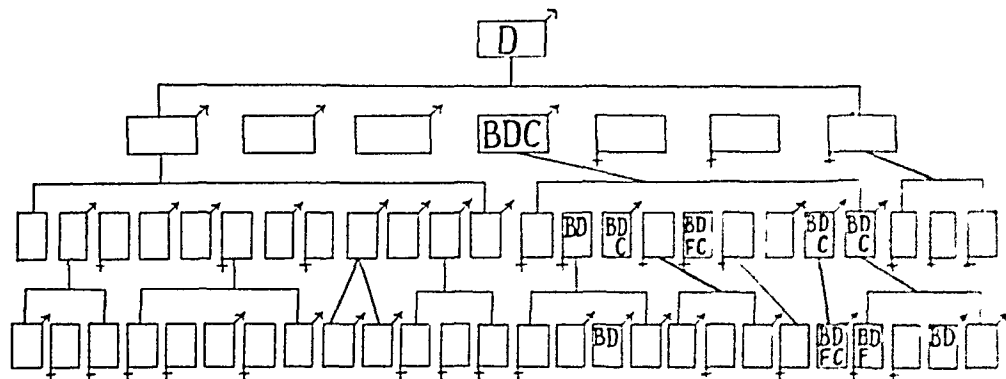


Fig 2—Family diagram, family group I. B indicates blue scleras, D, deafness, F, fractures, C, spinal deformities.

small boned and weighed 130 pounds (59 Kg). The scleras were of a striking blue color and of metallic appearance. There was grade 2 scoliosis, with the convexity directed toward the left, and grade 1 lordosis. There was grade 1 edema of both feet and legs, extending upward to a point 10 cm below the knees. Pes planus, grade 4, was present as a result of ligamentous relaxation. Varicosities of the veins of the lower extremity were noted. There was poor tissue turgor and the muscles were flabby and hypotonic. The deafness was bilateral and of the conduction type. The result of Rinne's test was positive and Weber's test showed lateralization of sound to the affected side.

The hemoglobin concentration was 93 per cent, the red blood cells numbered 4,000,000 per cubic millimeter and the white blood cells 10,500. Urinalysis gave normal results. The Kahn reaction of the blood was negative. Phenolsulfonphthalein and concentration tests yielded normal results. A bromsulphalein test gave a normal result. Roentgenograms of the spine showed thinning of the bodies of the eleventh thoracic and first lumbar vertebrae, accompanied by scoliosis. The extremities were normal. A diagnosis of osteogenesis imperfecta (latent form) was made.

CASE 2—L O, a woman aged 37, was a sister of the previous patient. Blue sclerotics had been present from birth. She had sustained her first fracture at the age of 3 years. From this time until the age of 18 the patient had had an average of two fractures a year, the bones of the lower extremities being most frequently involved. The tibia, fibula, femur, radius, ulna and humerus suffered multiple fractures. In all, the patient had had twenty-seven fractures. The tibias showed anterior bowing or saber-like deformity. At about the age of 12 years the patient had become hard of hearing. At the time of this study there was bilateral deafness of the conduction type. She heard fairly well over the telephone, however, and she was a switchboard operator, having served in this capacity for the previous seventeen years. At the age of 10 years she could not walk without the aid of crutches, and at the age of 18 years it was necessary for her to use a wheel chair in order to get around. Her scleras were intensely blue, her bones were very small and short, and there was a curvature of the spine. She had had no fractures since the age of 26.

Three other members of this generation, 2 brothers and 1 sister, likewise had the blue scleras, otosclerosis with bilateral deafness, spinal curvatures, short stature and small bones. The deafness made its appearance early. There are 4 other members who are normal. None of the aforementioned 3 members has had fractures, and there are no deformities other than the curvatures.

All 3 of these persons married. In the case of 1 brother, R O, 4 children were born, 2 normal and 2 with blue sclerotics. The latter 2 children are hard of hearing, deafness having made its appearance at about the age of 8 years. Neither one has curvatures, and only 1 has had fractures. The latter, a girl, has had a total of six fractures, the first making its appearance at the age of 2 years. She is now 12 years of age and has not sustained any fractures for the past two years. Calcium and vitamin D were prescribed and roentgen therapy employed. Four of the fractures were confined to the lower extremities. Good approximation was obtained in every instance, and no deformity resulted.

Two other members of this generation, cousins of the children just described, have blue sclerotics and are deaf, but only 1, a boy, has had fractures. He has had two fractures, both making their appearance before the age of 1. He is now 4 years old.

CASE 3—D O, now dead, was the father of the patients in cases 1 and 2. He was one of 7 children, 4 boys and 3 girls. He was the only member of the family affected. Deep blue sclerotics were present from birth, deafness made its appearance at the age of 10 years, was progressive and rendered him almost totally deaf in later life. He had a curvature of the spine, and there was a characteristic limp in his gait. There was no history of fractures. He was born in Ireland and came to this country at about the age of 25. No history of his father could be obtained, other than the fact that he was deaf and very short.

Comment on Family Group I. This family group is illustrative of the hereditary tendency of the syndrome. It is transmitted as a dominant mendelian factor, the blue sclerotics being a more dominant

factor than were the other components of the syndrome. From the discussion of the cases it is readily seen that different factors, as well as various degrees of the same factor, are inherited. What are perhaps two outstanding characteristics in this group are the latent character of the bone conditions and the high incidence of deafness with its early appearance in every case. Three of the cases are representative of the van der Hoeve syndrome. The intensity of the blue color of the scleras is not indicative of the severity of the bone condition as is commonly supposed.

Family Group II—The seat of origin of the condition in this family was Germany, in 1770 (fig 3). F. B. had blue sclerotics and was deaf, he had 4 children, 3 girls and 1 boy, all of whom had blue sclerotics and were deaf. Deafness did not manifest itself until the

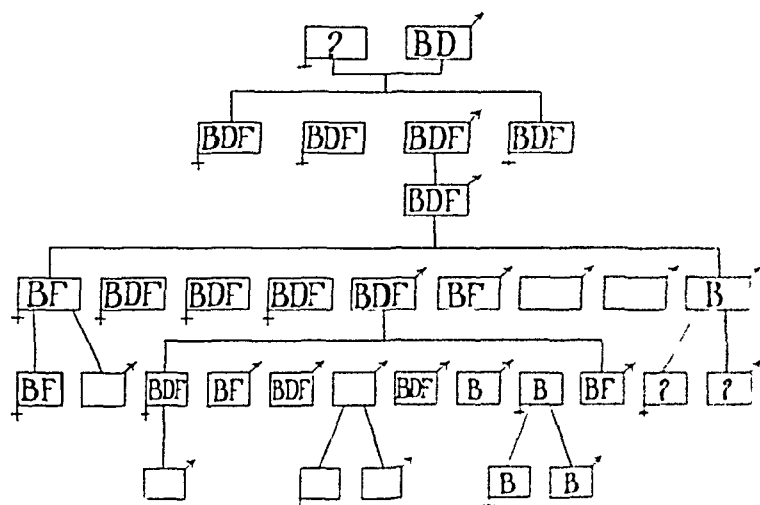


Fig 3—Family diagram, family group II. B indicates blue scleras, D, deafness, F, fractures.

third decade. A history of fractures also was obtained for all the 4 children. A discussion of the 3 daughters will be reserved until family group III is discussed, since all 3 married into this family. The boy, J. B., had 1 child, a son, who had blue sclerotics deep in color, was extremely deaf and had one or two fractures in boyhood. He had 9 children. Seven had blue scleras, 4 of the 7 became deaf between the ages of 25 and 40, and 6 of the 7 had fractures. The incidence of fractures in this family group was not so great. The greatest number that any person had was five. Four girls and 3 boys were affected. Only 2 of the boys and 1 girl married. The girl gave birth to 2 children, 1 of whom had blue scleras and a number of fractures. No information could be obtained concerning the first son. The second son had 8 children, 6 boys and 2 girls. Seven of them had blue scleras, and 5 sustained fractures. Three were deaf. Three of this group

married. One was normal and had 2 children, both of whom were normal. Another, a daughter with blue scleras, had 2 children, both of whom have the blue scleras but as yet no fractures. They are now aged 2 and 4 years, respectively. A third, another daughter, with the three major characteristics, had 1 normal child, a son.

Comment on Family Group II. The strong hereditary tendency is observed in this family group. Out of a total of 33 members, 23 have the blue scleras, 16 of whom sustained fractures and 12 of whom were deaf. The deafness was strongly inherited, appearing in the second or third decade and rendering the persons almost totally deaf at the age of 45 to 50. The fracture diathesis, while present in 50 per cent of the family group, tended to be less frequent and less severe than usual. This group is likewise representative of the van der Hoeve syndrome.

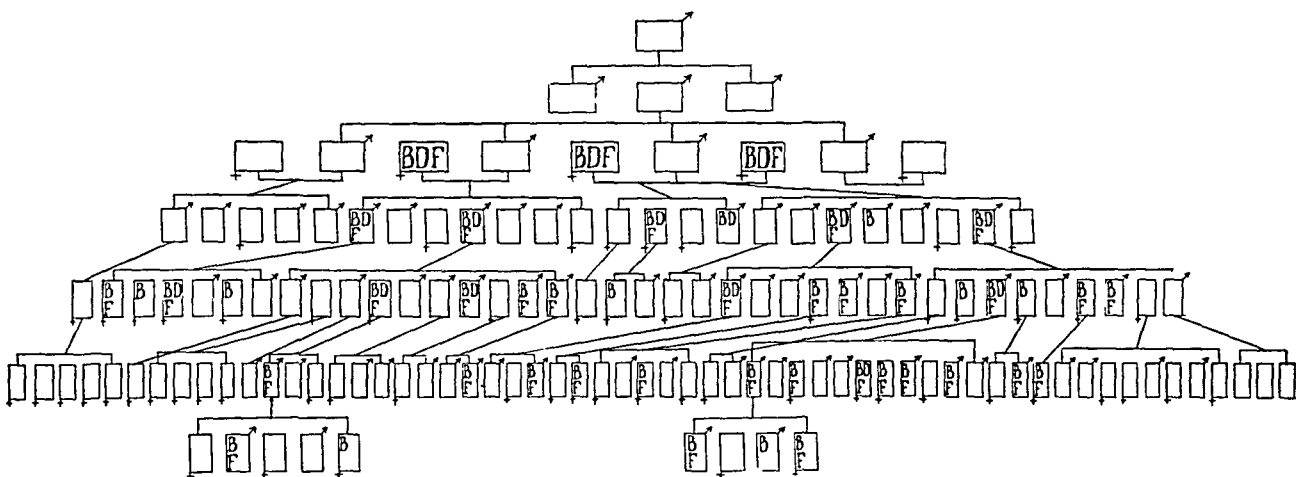


Fig 4—Family diagram, family group III. B indicates blue scleras, D, deafness, F, fractures.

Family Group III.—Osteogenesis imperfecta first made its appearance in this family in Maryland and Virginia in 1808 (fig 4). The ascendants were traced for three generations, to 1735, in England, and the history was entirely negative. There were 4 sons in the third generation, all of whom were normal. Two of the sons married women whose history was also negative for the disease and one of whose families, traced for three generations, were likewise normal. The third son, W P, married N B, one of the 3 sisters of family group II, of their 7 children, 2 had the blue scleras, brittle bones and deafness. The fourth son, W H P, married S B, the second sister of family group II, and 2 children out of 4 inherited the condition. After the death of his first wife, W H P married J B, the third sister of family group II, and of 8 children, 6 boys and 2 girls, 3 boys had blue scleras and brittle bones and 2 were deaf. One of the sons in this generation

had as many as seventy-five fractures. He lived to be 89, and the tendency to fracture persisted until the time of his death. During the last fifteen years of his life he set his own fractures.

Five of the 7 children in this generation who inherited the condition married, and in the next generation there was a total of 38 members, 18 of whom inherited the syndrome. Only 5 of this generation were deaf, however. Eighteen members of this generation married, but 1 of them had no children and is not indicated on the chart, 8 of them had *osteogenesis imperfecta*. The members who were normal had a total of 28 children, all of whom were likewise normal. A total of 29 children were born to the 8 affected members, and the condition was inherited by 13 of this group. All of these members had blue sclerotics and fractures, and 1 became deaf. The oldest member, however, is only 30, so that for the present a definite conclusion cannot be drawn in relation to the factor for deafness. Two cases in this group are of particular interest and will be considered in some detail.

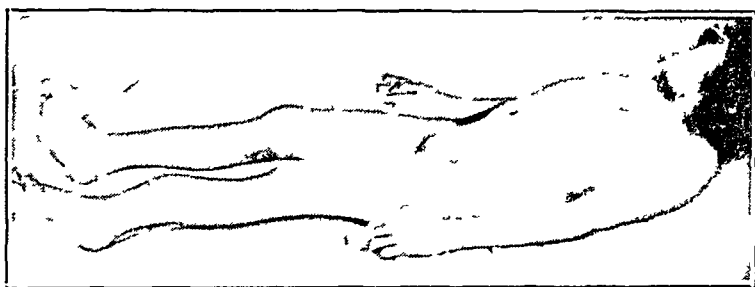


Fig 5 (case 4) —A completely incapacitated girl of 9 years with a history of many fractures

CASE 4—A girl aged 9 had blue scleras from birth. She sustained her first fracture at the age of 2. This was a transverse fracture of the midportion of the tibia and fibula of the left leg (fig 1). One year later the tibia and fibula of the left leg were again fractured, at a point 1 inch (2.54 cm) higher than the previous fracture. Within five months and again in one year fractures occurred in the left leg, the points of fracture being through previously fractured areas. Since then, she has had sixteen other fractures, two confined to the left femur and the rest in the tibia and fibula of the left leg. The slightest trauma was responsible for all the fractures. The child has been unable to stand or walk for the past five years (fig 5). Except for the use of cod liver oil, no medical therapy has been instituted. The child weighs 60 pounds (27.2 Kg), is 46 inches (116.8 cm) tall, is small boned and has pale blue sclerotics and saber deformity of the left leg. There is well developed bilateral pes planus but no scoliosis or deafness.

CASE 5—R. P., aged 12, a sister of the previous patient, had blue scleras from birth. The first fracture occurred at the age of 1½ years. She has had twenty-five fractures since, all confined to the lower extremities, with the majority in the femurs. There have been no fractures for the past two years. She, like her sister, has been unable to stand or walk since she was 2 years old. The only

had 1 child, a boy, who had blue scleras and who also was totally deaf and sustained several fractures. There were 4 children in the third generation, 1 of whom inherited the disease from his father. His scleras were blue, he was deaf, and according to his granddaughter every bone in his body except those of the pelvis and spine had been fractured at one time or another during his life. There was an only child in the fourth generation, and he likewise inherited the syndrome. He broke his legs seven times from slight falls during his childhood, and progressive deafness made its appearance in the third decade, as it had done in the others.

In the fifth generation of this family group there were 5 children in a family of 8 who inherited the blue scleras. Three of the 5 have had fractures, and 2 of the oldest ones affected are slightly deaf. Two of the children have had three fractures each, always in the lower extremities. The third child will be considered more in detail.

CASE 6—V C, aged 25, has had blue scleras from birth. At the age of 2 years she sustained a fracture of the femur from a trivial fall while she was toddling about the floor. A short time later another fall caused a fracture of the tibia in the opposite leg. Since then she has sustained numerous fractures of the lower extremities, both femurs and both tibias and fibulas being involved at different times making a total of twenty-five fractures in all, and always from some slight fall or other trivial cause. Considerable angulation occurred at the fracture sites, with resulting deformity, so that the patient could scarcely walk. Orthopedic measures were then instituted, and several osteotomies were performed, accompanied by straightening of the legs and the application of braces to hold them straight. The braces were kept on for two years, during which time the patient was able to walk some distance to school every day. Four weeks after the removal of the braces the patient was able to walk as well and as readily as a normal child. This child was converted from what seemed an almost hopeless cripple into a bright and happy girl with perfectly good, useful legs.

The fractures in all 3 children had their onset at the age of $1\frac{1}{2}$ years, and the tendency toward fracture ceased at the age of 14. This is a characteristic occurrence in the majority of cases, but it is unusual to observe it repeatedly in a single family.

There are 2 of 4 members of the sixth generation affected. One is 3 months old and has the blue scleras, the other, 2 years old, has the blue scleras and has had one fracture. The mother of the 1 normal child is the patient, V C, in case 6.

Comment on Family Group IV. The distinguishing characteristics in this family group were the multiplicity and extensiveness of fractures in the case of the son of the third generation, the high incidence of deafness, inherited as a 67 per cent factor by those who are affected, and the favorable response of the patient V C (case 6) of the fifth generation, to orthopedic treatment.

Family Group V—Blue sclerotics made their appearance in this family in Washington, D C, in 1904 The affected person, now 33, was born at full term with normal delivery, was breast fed and had a normal infancy and childhood The scleras were blue from birth She has never had a fracture, and there is no impairment of hearing She has 1 child, a girl aged 8 years, who has had four fractures and whose scleras were likewise blue at birth The child was born at full term with forceps delivery after a twenty-four hour labor, was breast fed and had a normal infancy She suffered her first fracture at the age of 3 She has had none since March 1937 The child has had roentgen therapy and has taken cod liver oil and calcium lactate No deformity is present, and there is no impairment of hearing The maternal and paternal ancestors were traced for two generations, with negative results No history could be obtained beyond the two generations

Comment on Family Group V There is no doubt that the child has the syndrome of Lobstein, consisting of blue sclerotics and brittle bones, and it is evident that she inherited the condition from her mother, who has only the blue scleras Since no other history of the disease could be obtained, it must be admitted either that her mother was the first one in the family to be affected or that the disease skipped two generations, as occasionally happens⁷

Family Group VI—The first and only instance of osteogenesis imperfecta in this family occurred in Washington, D C, in 1904

CASE 7—N B, a white physician aged 35, married, who was born at full term with normal labor and delivery, has had china blue sclerotics from birth His first fracture made its appearance at the age of 10 months From then until the time of puberty he sustained thirteen or more fractures, all confined to the lower extremities and involving the tibias, fibulas and femurs Slight trauma provoked the fractures in every instance Two years after the onset of puberty the tendency for spontaneous fractures ceased, and the patient, being very active and energetic, engaged in all forms of sports, including football As a result of this activity he suffered seven fractures, all of which were confined to the upper part of the body and included the radius, ulna, clavicle and nose After his athletic activities, there was a latent period of about ten years during which no fractures occurred His next fracture was the result of a fall, causing him to break the left ulna His last episode of fractures happened seven years ago, when a friend jokingly slapped him on the back and broke three ribs

A careful search of his ancestry, both maternal and paternal, was made The history went back three generations on the maternal side and five generations on the paternal side The ancestral, as well as the family, history was negative, the patient's own brothers were normal The patient has no children He comes from a good family stock and is well educated, holding several college degrees The present weight is 160 pounds (72.6 Kg), the height is 63 inches (160 cm), the bones are small, but the general development is good China blue sclerotics and saber-like deformity of the left forearm are obvious There is no other deformity, and no impairment of hearing exists

Comment on Family Group VI An isolated instance of the disease, such as this case represents, is extremely rare,²² and in view of the hereditary and familial nature of the disease its occurrence requires an explanation There are three possibilities (1) that the disease is not always hereditary, (2) that more than two generations may be skipped and (3) that this case represents the source of origin of the disease in this family The last possibility is the more likely, since obviously the disease must make its initial appearance before it can be transmitted If there are any children in this family, half will be expected to inherit the condition

Family Group VII—Only 1 member of this family group was found to have the disease The ascendants, descendants and collaterals were traced for three generations on both the maternal and the paternal side The patient herself, who was born in Virginia in 1896, had 7 siblings, all of whom were normal

CASE 8—R T, an unmarried white woman aged 44, was first seen in the medical clinic of the dispensary of the Georgetown University Hospital in March 1940 Her chief complaint was of dizziness, ringing in the ears and slight nausea, dating back ten years Attacks of these symptoms had occurred periodically, without apparent cause About six months after the onset of tinnitus in the left ear the ringing was noticed in the right ear A slight degree of deafness had developed in the left ear when the patient was 25 This was followed five years later by impaired hearing in the right ear The deafness became progressive until now there were total loss of hearing in the left ear and marked impairment in the right

The patient had been small and delicate from birth She had had a normal birth and infancy and was bottle fed She had had the usual diseases of childhood but had never been seriously ill Vision had been poor for the past ten years The patient had been hospitalized four years before for two fractures received in an automobile accident She had been examined in the eye and ear clinics and in the neurologic clinic twice during the preceding seven years A diagnosis of chronic otitis media and labyrinthitis with Ménière's syndrome had been made two years before

The patient weighed 83 pounds (37.6 Kg) and was 5 feet (152 cm) tall The following abnormalities were noted metallic blue scleras, small bones, pigeon-shaped chest, slightly enlarged knee joints, anterior bowing of the left leg, club-shaped deformity of the left foot, hypermotility of the joints, prominence of the superficial veins of the legs, extremely poor tissue turgor and muscle tone and bilateral deafness of mixed type Air conduction showed a greater degree of impairment than bone conduction The result of the Rinne test was negative, and Weber's test showed lateralization of sound to the left Schwabach's test showed reduction in both high and low tones, the tone limit

²² Parnall, E Osteogenesis Imperfecta, J Bone & Joint Surg **19** 228 (Jan) 1937

being reduced from above and below. Concomitant divergent strabismus of the alternating type was present.

The results of urinalysis and a hemogram were normal. The Kahn and Wassermann reactions of the blood were negative. Roentgenograms of the left leg made at the time the fractures were sustained showed a transverse fracture of both the tibia and the fibula an inch (2.5 cm) below the knee joint. There was an extreme degree of thinning of both bones, the peculiar cross striations of osteogenesis imperfecta were present but not marked.

Comment on Family Group VII. This isolated case well exemplifies the van der Hoeve syndrome. The deafness not only was progressive and severe but was accompanied by tinnitus, vertigo and nausea, which were very disturbing. The main symptoms were the result of involvement of the eighth nerve, due to the otosclerosis that often accompanies the disease. Although the roentgen appearance of the bones was typically that of osteogenesis imperfecta, the bone condition remained latent and spontaneous fractures did not occur. This persistence of the osseous features, even in latent form, until the age of 40 is extremely unusual. Evidently, either the blue sclerotics had gone unrecognized all the while, or if recognized they were not regarded as important enough to warrant comment.

SUMMARY AND CONCLUSIONS

Osteogenesis imperfecta is a hereditary and familial disease and is transmitted as a dominant mendelian factor. It is a hereditary mesenchymal hypoplasia due to a disturbance of the gene or genes that determine normal mesenchymal development.

The most important features representative of the clinical manifestations of the disease are (a) blue sclerotics, 100 per cent, (b) brittle bones with multiple fractures, 65 per cent, and (c) otosclerosis with progressive deafness, 43 per cent. The most common deformities are spinal curvatures, saber-like deformity of the long bones and pes planus.

Blue sclerotics may be the only manifestation of the disease, and when associated with a history of other manifestations in other members of the family group they are pathognomonic of the syndrome. In the absence of obvious causes of blueness of the scleras they are pathognomonic even when such a family history is not obtainable.

The intensity of the blueness of the scleras is not necessarily an index of the severity of the disease.

Certain families have a predilection in regard to the frequency, severity and time of onset of otosclerosis.

Certain families have a predilection in regard to the incidence of brittle bones with multiple fractures, but there is considerable variation in the occurrence of this factor even in individual families.

With few exceptions there is a marked remission of the tendency toward fracture at the onset of puberty. Adults rarely show the roentgenographic features of the disease. The osseous abnormality is the only reversible feature of the disease.

Multiple fractures at the same site often result in deformity and incapacitation.

The roentgenographic appearance of the affected bones is characteristic, consisting of diminution in size of the diaphysis, great thinness of the cortex and presence of peculiar cross striations.

The early institution of proper orthopedic measures can do much to relieve the crippling nature of the disease.

The economic background does not play a predisposing role in the appearance of the disease.

Of 255 members of 7 family groups, there were 91 who were definitely known to have the disease. The existence of the disease in some of these family groups was traced back for six generations. In each of 2 family groups, only 1 person with the disease could be found, and in a third only a mother and her daughter were discovered to have the disease.

Although there are three recognized forms of the disease, every case in this series is an example of the osteogenesis imperfecta tarda or the infantile type, with the appearance of Lobstein's syndrome as a 57 per cent factor and van der Hoeve's syndrome as a 43 per cent factor.

The prenatal and postnatal use of thymus extract has been suggested.

Future progress in the treatment of the disease may depend on a better understanding of the principles of genetics and eugenics.

NOTE—Since this paper was accepted for publication we have discovered a new family group in which 7 cases of osteogenesis imperfecta were found. The condition made its appearance in this family in North Carolina, in 1870. Three members of the first generation had blue sclerotics and were deaf, but a history of fractures could not be obtained. Four members of the second generation inherited the condition, all had blue sclerotics, 3 were deaf and 2 had fractures. One of these 4 was the patient who applied for examination. She had blue sclerotics and was deaf. She has had 2 children, who are normal. Another member of the same generation, who had blue sclerotics and deafness, had 2 children, who are normal. Dislocations were a prominent feature in this family group. Three members of the second generation had dislocations of the left shoulder joint. The patient who was examined had four dislocations, a sister had seven dislocations and a brother had one dislocation.

OBESITY

ITS PATHOGENESIS, ETIOLOGY AND TREATMENT

JULIUS BAUER, M D

HOLLYWOOD, CALIF

CRITIQUE OF THE CURRENT ENERGY THEORY OF OBESITY

The usual conception of obesity, particularly in the United States, is that it is always caused by an imbalance between intake and output of energy "Exogenous or simple obesity is the result of maladjustments between food and exercise. Endogenous obesity is due to the lowered metabolism resulting from a disturbance in hypothalamic or endocrine functions, e g, gonads, pituitary, or thyroid" (Best and Taylor,¹ page 981)

According to Means,² both the exogenous and the endogenous type of obesity are due to a simple disproportion between the intake of food and the energy requirement of the body. Endogenous obesity is endogenous merely in the sense that in the creation of such a disproportion a fall in the rate of oxidation in the body plays a role. A much greater proportion of obesity, however, is of the exogenous type. As a matter of fact, the ratio between total caloric intake and total caloric output is what counts. Persons who gain weight readily, even though they apparently do not eat to excess, are usually phlegmatic, they worry less, sleep either longer or more soundly and when at rest relax more completely than persons of the normal, or thin, type.

This conception of obesity has been substantiated chiefly by Newburgh and Johnston³ and almost universally accepted on account of its promulgation by leading authorities, yet it is not satisfactory, for the following reasons

1 As nobody is in doubt that the law of conservation of energy holds also for the animal body and as it is an established fact that any surplus of intake of energy as compared with its output leads to accumulation of

From the Department of Medicine of the Louisiana University School of Medicine

1 Best, C H, and Taylor, N B. The Physiological Basis of Medical Practice, ed 2, Baltimore, Williams & Wilkins Company, 1939

2 Means, J H, in Cecil, R L. Textbook of Medicine, ed 4, Philadelphia, W B Saunders Company, 1937, p 659

3 Newburgh, L H, and Johnston, M W. The Nature of Obesity, J Clin Investigation 8 197, 1930, Endogenous Obesity A Misconception, Ann Int Med 3 815, 1930

fat in the body, obesity may be called the result of an imbalance between energy intake and energy output. Such a statement is a tautology rather than an explanation of the nature of obesity. Many authorities have emphasized the fact that normal persons must be protected against such an imbalance in some way, otherwise the majority would become obese. As a matter of fact, they are well protected. The automatic regulation of intake and output of energy is controlled rather precisely by a number of so-called general feelings, such as appetite, hunger, satiety and the desire for muscular activity or for its restriction, the last being due to fatigue, weakness or exhaustion. But it is not only this nervous-regulatory mechanism which tends to maintain the body weight. The thyroid, as well, adapts its activity to the requirement, it restricts the production of hormone and herewith the oxidative processes in the body if an insufficient amount of food intake threatens the maintenance of the balance, and it functions in excess if overfeeding is going to increase unduly the body weight. This adaptative power characterizes the living organism as compared with a physicochemical machine.

2 If exogenous, or simple, obesity is defined as the result of maladjustment between food and exercise, then it requires a breakdown of the mentioned regulatory mechanism, which is represented by endogenous functions of the living body. In other words, an exogenous obesity is always an endogenous one also. I am very much in doubt whether it is possible to produce obesity artificially in a normal person. What may be produced by artificial overfeeding or artificial restriction of muscular activity is a temporary overweight but not a persisting obesity. If I may use this formula, the relation of such a temporary overweight to obesity is rather similar to the relation of a leukocytosis to a leukemia. The capacity and tolerance of the gastrointestinal tract and the automatic regulations of a normal organism will prevent the evolution of a true obesity. All minute calculations concerning the intake and output of energy hold only for a physicochemical machine—all other conditions being equal—but they fail to be applicable for definite conclusions to a living organism with a far developed adaptative power.

3 To attribute stoutness to an increased appetite resulting either from faulty habits of eating (von Noorden, Joslin, Lichtwitz, Labbé and others, cited by Bauer ⁴) or from a hereditary abnormality (Wilder ⁵) is not quite justified. Appetite is a general feeling serving the organism to build up the necessary quantity of body tissue and to maintain the

4 Bauer, J. Endogene Fettsucht, Verhandl. d. deutsch. Gesellsch. f. Verdauungs- u. Stoffwechselkr. 9:116, 1929.

5 Wilder, R. M. (a) The Regulation of the Weight of the Body, Internat. Clin. 1:30, 1932, (b) Disease of Metabolism. Review of Certain Recent Contributions, Arch. Int. Med. 61:297 (Feb.) 1938.

body weight at an approximately equal level. It is the requirement of the organism, both quantitative and qualitative, which rules the appetite. Appetite for sodium chloride or for calcium, for instance, is influenced by the functional condition of the adrenal or the parathyroid glands, respectively, as Richter and Eckert⁶ demonstrated in interesting animal experiments. Putnam, Benedict and Teel⁷ produced typical acromegaly and gigantism in a young female dog by treating it for fourteen months with intraperitoneal injections of an extract of the anterior lobe of the beef pituitary containing the growth-promoting principle. The dog acquired a ravenous appetite, but no one is likely to assume that daily intraperitoneal injections of pituitary extract stimulated it. Every one will rather assume that the injections provoked a tendency toward increased proliferation of cells, leading to gigantism and acromegaly, and that this increased cellular activity required a greater amount of energy and in turn led to an unusual intake of foodstuffs. The increased appetite is therefore to be looked on as an interposed factor not directly influenced by the injections but indispensable for the realization of the gigantism and acromegaly which the growth-promoting substance finally produced.

Reed, Anderson and Mendel⁸ found that rats treated with thyroxin lost weight in spite of eating almost double (12 Gm of food daily as compared with 7 Gm for the controls). Administration of thyroxin undoubtedly increased the appetite, not directly but by the adaptation of the organism to the increased requirement of food. Every physician with any experience knows that the changes of the basal metabolic rate produced by a pathologic alteration of the thyroid are not followed regularly by corresponding changes of the body weight because of the individually different capacity of adaptation of the appetite to the requirement.

Although the existence of a primarily ill trained or hereditarily abnormal appetite causing obesity hardly can be disproved, there is no positive proof of its existence either, and many facts to be discussed here later argue against the validity of such a hypothesis. It is just as possible that an increased appetite is the consequence of the tendency of the body to gain in weight and that it represents only a necessary

6 Richter, C. P. Salt Taste Thresholds of Normal and Adrenalectomized Rats, *Endocrinology* **24** 367, 1939. Richter, C. P., and Eckert, J. F. Mineral Appetite of Parathyroidectomized Rats, *Am. J. M. Sc.* **198** 9, 1939.

7 Putnam, T. J., Benedict, E. B., and Teel, H. M. Studies in Acromegaly. Experimental Canine Acromegaly, Produced by Injection of Anterior Lobe Pituitary Extract, *Arch. Surg.* **18** 1708 (April) 1929.

8 Reed, L. L., Anderson, W. E., and Mendel, L. B. Factors Influencing the Distribution and Character of Adipose Tissue in the Rat, *J. Biol. Chem.* **96** 313, 1932.

means for the realization of such a tendency. This would be a complete analogy to the mechanism operating in artificial acromegaly which I have just discussed.

4 The same reasoning holds true for the decreased output of energy in many cases of obesity. The obvious restriction of muscular activity, the avoidance of any superfluous movement, the more or less marked laziness noted in many such cases may be the consequence rather than the cause of the overweight. Only infrequently do persons bedridden for some surgical reason, such as a fracture, acquire more than a slight and temporary overweight during the time of their inactivity. Such a forced restriction of muscular activity does not result in real obesity. An obese man who avoids unnecessary movements is behaving like a normal person who carries about a more or less heavy load. Thus the tendency toward a decreased output of energy is more the consequence than the cause of obesity.

5 Endogenous obesity is considered as an imbalance between intake and output of energy due to a lowered metabolism. Such a mechanism is possible and does not at all mean, as Wilder⁵ claimed, that the law of conservation of energy fails to function. However, is this mechanism actually operating in cases of endogenous obesity?

(a) The simplest and most common explanation of the imbalance was formerly the assumption of a diminished basal metabolic rate in cases of endogenous obesity with a subsequently diminished energy requirement. No doubt a person with a lowered basal metabolic rate will increase his weight *ceteris paribus*, that is, if all other conditions remain unchanged. Increasing weight is therefore a frequent symptom in patients with hypothyroidism, and if it does not appear in all cases, it is because the status quo of other conditions is not maintained. Some few cases of obesity are to be explained by a lower basal metabolic rate, and in such cases overweight is actually one of the symptoms of hypothyroidism. In the majority of obese patients, however, one fails to detect a decreased basal metabolic rate and therefore a diminished requirement of foodstuffs.

I do not wish at this point to enter into a discussion of the difficulties of obtaining reliable values for the basal metabolic rate in obese persons but wish merely to emphasize the fact that in the great majority of such persons the rate has not been found to be diminished. In addition, one must recall the not infrequent cases in which even abnormal leanness is associated with a markedly diminished basal metabolic rate as, for instance, in Simmonds' pituitary cachexia.

(b) When it became obvious that it was impossible to explain an apparent endogenous obesity by a diminished basal metabolic rate an attempt was made to explain the imbalance on the basis of the not infre-

quent reduction of the specific dynamic action of food. If the intake of foodstuffs does not increase the oxidations, as under normal conditions, then, *ceteris paribus*, overweight must result. But, again, it is the balance of other factors which as a rule is disturbed by adaptative alterations of the body. Persons with a decrease in or practically an absence of the specific dynamic action of food are to be met with not only among the obese but also among the lean or even the cachectic. In addition, the possibility has to be emphasized that a diminished specific dynamic action could just as well be the consequence of obesity, for the reason that the transformation of carbohydrate into oxygen-poorer fat would not require any further intake of oxygen, and in this way the consumption of oxygen would be diminished.

(c) Efforts to prove a particular economy of muscular activity in obese persons (Gessler⁹) have failed. The working muscle of an obese person does not require less energy than that of a normal one.

A lowered metabolism has, therefore, not been proved to be the cause of endogenous obesity, except in those infrequent cases in which obesity is one of the symptoms of hypothyroidism. In those cases of endogenous obesity in which a disturbance of the functions of the hypothalamus, the gonads, the adrenal glands or the pituitary is apparently the cause of the endogenous obesity, a lowered metabolism has not been proved to be operating in the pathogenesis.

6 If a simple disproportion between the intake and the output of energy were the actual cause of obesity, then it would be necessary to discriminate between the different foodstuffs only as far as their caloric value is concerned. For the purpose of transformation of energy a calory is a calory, for the purpose of treating obese persons it is not. The experienced practitioner will reduce the intake of carbohydrates and fat but will not reduce the proteins to the same extent. On the contrary, an undue reduction of the protein calories will not only endanger the integrity of the cells but even inhibit a proper reduction of the body weight. It is not only the amount of calories but also the quality of equicaloric amounts of foodstuffs that counts.

7 Still another factor not to be explained from the point of view of a mere energy imbalance is the abnormal water and salt metabolism encountered, as a rule, in the more pronounced cases of obesity and lipomatosis (Zondek, Bauer⁴). Persons with such a metabolic disturbance frequently pass highly concentrated, scanty urine, a total amount of 300 to 500 cc per day, with a specific gravity of 1.030 to 1.035, is not unusual. If they are given 1,000 to 1,500 cc of water over a half-hour period, they usually show a marked retention, elimination does not take place in the normal time of four hours, but may be

9 Cited by Bauer⁴

delayed twenty-four hours or longer (Vollhard's test) If they are given 10 Gm of sodium chloride, they usually retain the salt for two or three days, instead of eliminating it within the normal time of twenty-four hours

My former co-worker dell'Acqua¹⁰ determined simultaneously the sodium chloride content of capillary and of venous blood from thirty to one hundred and twenty minutes after the intake of 10 Gm of sodium chloride in 125 Gm of water In some persons with uncomplicated obesity (6 among 13 examined), he found notably higher amounts of sodium chloride in the capillary than in the venous blood the difference ranging from 40 to 15 mg per hundred cubic centimeters Similar differences have been encountered only in persons with certain types of renal lesions or with diabetes The ingested sodium chloride is retained abnormally in the tissues

Since the retention of sodium chloride and water in obese persons is not caused by impairment of renal function it must be due to an abnormal avidity of the tissues for these substances That they are chiefly retained in the cutaneous and subcutaneous connective tissue seems probable from the studies of my former collaborator Recht¹¹ The McClure-Aldrich test is a delicate indicator of the water content of the skin, the greater the content the more rapid are the resorption and disappearance of an intracutaneous wheal of a physiologic solution of sodium chloride In a series of such tests Recht found a diminished resorption time in obese persons and also noted marked regional differences in the resorption time in persons with more localized lipomatosis Those parts of the body surface containing larger amounts of fat showed a more rapid disappearance of the wheals A dehydrating injection of a diuretic containing mercury, such as salyrgan, which in some cases is followed by a rapid loss of several pounds, was much less effective in the lipomatous regions of the body than in the others In other words, the tendency of the subcutaneous connective tissue to accumulate larger amounts of fat is apparently associated with a tendency to store water in these particular regions of the skin In some cases, Recht found the antidiuretic action of posterior pituitary U S P to be unusually intensive and prolonged

All these statements concerning the water and salt retention in obese persons have been completely confirmed by Wohl¹² in this country

10 dell'Acqua, G Ueber Austauschvorgänge zwischen Blut und Gewebe die capillar-venöse Differenz des NaCl-Spiegels im Blute, *Klin Wchnschr* 8 1709, 1929

11 Recht, G Ueber den Wassergehalt der Haut bei Fettsüchtigen Untersuchungen mit der Quaddelprobe, *Klin Wchnschr* 8 1748, 1929

12 Wohl, M G Metabolic Changes and Treatment of Obesity *Am J M Sc* 183 613, 1932

namely, the retention in the Volhard test, the high water content of the skin as demonstrated by McClure and Aldrich's test and the difference in the levels of sodium chloride in the venous and the capillary blood after the administration of 10 Gm of sodium chloride Wohl found such differences as great as 100 mg¹³

8 Hetherington and Weil¹⁴ studied the chemical composition of the bodies of rats exhibiting pathologic obesity resulting from hypothalamic injuries Calcium and phosphorus were considerably diminished and iron frequently diminished in percentage amounts as compared with values for the controls They stated

It would seem that besides the obviously disordered fat metabolism in these cases of adiposity there is a more widespread upset of the body's physiological economy which takes in the calcium, phosphorus and iron exchanges, and possibly other factors as well

The mere energy concept of obesity cannot account for these changes

9 All the more does this hold true if the regional differences of fat deposition are considered The difference in distribution of adipose tissue in both sexes does not need further discussion In women rather well defined varieties of fat deposits are met with¹⁵ Most frequently, in about 90 per cent of all women, the distribution of fat is around the hips and on the thighs, the lower part of the abdomen, the buttocks and the back, as illustrated by Rubens' favorite subjects One may therefore call this variety the "Rubens type" It corresponds to what is also called the "gudle type" of fat distribution Other women show a particular accumulation of fatty tissue in the trochanteric region, which protrudes from the outline of the body One may call this variety of obesity the "breeches" or the "trochanteric" type of fat distribution Some women are annoyed by a more or less marked accumulation of fat in the lower extremities, usually extending from the hips to the knees or the ankles In some women the excess fatty tissue is limited to the calves or ankles In the more pronounced cases of this "inferior" type of fat distribution, the fatty masses are arranged like clusters and the skin on the surface of the thighs is subsequently covered with dimples The opposite, or "superior" type of fat distribution is seen in women with relatively slender legs and abdomen and rather marked accumulation of fat in the back, the upper parts of the arms, the breasts, the neck

13 Wohl did not mention that his studies are merely a repetition and confirmation of the work done by dell'Acqua¹⁰ and Recht¹¹ in my hospital in Vienna, although he was familiar with their work

14 Hetherington, A W, and Weil, A The Lipoid, Calcium, Phosphorus and Iron Content of Rats with Hypothalamic and Hypophyseal Damage, *Endocrinology* 26 723, 1940

15 Bauer, J Ueber Fettansatz, *Klin Wchnschr* 1 1977, 1922

and the face. Sometimes the unusual accumulation is limited to the breasts. As a matter of fact, there are also borderline conditions and combinations of these pure types.

The localized accumulations of fatty tissue are usually described as lipomatosis, but it must be understood that there are no sharp limits between a lipomatosis and a more or less generalized obesity. The mere fact that an abnormal accumulation of fat may show such different localizations must bring into the discussion of the pathogenesis of obesity another factor besides energy imbalance.

That the current, mere energy conception of obesity is unsatisfactory is a feeling expressed by several authorities in this country. Christian,¹⁶ for instance, declared

We must acknowledge that in some cases of obesity the cause is obscure. To say that there is one essential cause, overeating, does not explain all cases.

In "Oxford Medicine," Howard and Mills¹⁷ summarized their conception of obesity in the following words:

In conclusion, it would seem that, although the immediate exciting causes of obesity appear to be the ingestion of abnormal amounts of food, or of alcohol, or deficient exercise, yet the underlying basis is probably an obscure endocrine dystrophy, which overthrows the weight-regulating mechanism of the body by an imposed economy of metabolism and consequently excessive storage of fat.

THE BIOLOGIC THEORY OF CONSTITUTIONAL OBESITY

1 *Lipophilia*—Any satisfactory conception of obesity has, in my opinion, to consider first the unequal distribution of adipose tissue and consequently the variation in "lipophilia" of the subcutis in different parts of the body. In other words, a local factor must exist which influences the fat deposition in particular regions independently of the general energy balance or imbalance. The importance of such a local factor was first emphasized by Guenther (cited by Bauer¹⁸), who called the particular avidity to store fat "lipomatous tendency," or "lipophilia."

The enormous differences in lipophilia are obvious if one compares the cutaneous coverings on the forehead, fingers and lower part of the abdomen and back, even in the normal person. The lipophilia of a certain part of the skin tends to persist even when the skin is transplanted. Several observations in the literature¹⁵ prove this point. Burns on the back of the hand in young girls, for instance, were treated by grafts taken from the lower part of the abdomen. Many years later, when the

16 Christian, H. A., in Osler, W. The Principles and Practice of Medicine, revised by H. A. Christian, ed. 13, New York, D. Appleton-Century Company, Inc., 1938.

17 Howard, C. P., and Mills, E. S. Obesity, in Christian, H. A. Oxford Medicine, New York, Oxford University Press, 1940, vol. 4, pt. 1, p. 195.

18 Bauer (footnotes 4 and 15).

girls had grown and had acquired a certain degree of overweight, a second operation was necessary for the removal of the big fat pads which had developed in the grafted skin exactly as fatty tissue had developed in the skin of the lower part of the abdomen

The frequently entirely unequal distribution of adipose tissue in obese persons demonstrates that a local factor must be also involved in the pathogenesis of obesity, whatever the cause of the condition may be

The term lipophilia indicates a special tendency to deposit fat as well as a special resistance against the mobilization of fat from the adipose tissue. The existence of a different lipophilia in different regions of the body has been concluded from simple clinical evidence.¹⁹ It exists whether or not its biochemical mechanism can be elucidated. Fortunately, its existence and involvement in cases of obesity can be substantiated by a number of facts

Endeavors to demonstrate qualitative abnormalities in the metabolism of the obese subject have failed, according to Wilder's critical statement, in 1932.²⁰ Contradictory results have been obtained by different authors who have studied the respiratory quotient (Arnoldi, Wang, Strouse and Saunders²⁰, Hagedorn, Holten and Johansen²¹) and hunger lipemia (Kugelman²², Heteyni²⁰). Yet there have been found differences between obese and normal persons pointing toward an increased tendency of the former to store carbohydrates in the adipose tissue rather than glycogen in the liver and muscles. That carbohydrates are deposited in the adipose tissue in order to be transformed into glycogen first and then into fat has been proved by chemical and histochemical methods (Hoffmann and Wertheimer⁹, Loew and Krčma²³, Richter²⁴, Scoz, Baer and Boeri²⁵). Von Bergmann and Goldner,²⁶ Kugelman²² and Bientano²⁷ have made statements suggest-

19 The experiments of Reed, Anderson and Mendel⁸ showed that in rats such a local lipophilia has to be considered, too

20 Cited by Wilder⁵

21 Hagedorn, H. C., Holten, C., and Johansen, A. H. Pathology of Metabolism in Obesity, *Arch Int Med* **40** 30 (July) 1927

22 Kugelman, B. Untersuchungen zur Fettsucht als ein Problem intermediärer Stoffwechselstörung, *Ztschr f klin Med* **115** 454, 1931

23 Loew, A., and Krčma, A. Insulin und Nahrungsdepots, *Biochem Ztschr* **206** 360, 1929, *Inselorgan und Fettstoffwechsel der Leber*, *Klin Wchnschr* **11** 584, 1932

24 Richter, F. Experimentelle Untersuchungen über das Vorkommen von Glykogen im Fettgewebe, *Beitr z path Anat u z allg Path* **86** 65, 1931

25 Scoz, G., Baer, P., and Boeri, E. Insulina e ingrassamento, *Arch di sc biol* **22** 142, 1936

26 von Bergmann, G., and Goldner, M. Funktionelle Pathologie, eine klinische Sammlung von Ergebnissen und Anschauungen einer Arbeitsrichtung, Berlin, Julius Springer, 1932

27 Brentano, C. Beitrag zur Physiologie und Pathologie des Ketonkörperstoffwechsels, *Ztschr f klin Med* **124** 237, 1933

ing an abnormally low glycogen reserve in the liver and muscles of obese persons. Creatinuria, which Brentano stated to be an indication of glycogen mobilization in the muscles, is produced more easily and more rapidly in the obese than in the normal person by eliminating carbohydrate from the diet. Obese persons show a higher increase of lactic acid in the blood after slight muscular exercise than do normal persons, a fact which has also been confirmed by my former collaborator Medvei²⁸

Ketonemia and ketonuria depend on the relative proportions of fat and dextrose oxidized together, and more fat, as well as less dextrose, may account for ketosis. After a carbohydrate-free diet has been observed, the ingestion of olive oil increases the amount of ketone bodies in the blood of an obese person more markedly than in that of a normal one (Kugelman²², Lauter and Neuenschwander-Lemmer²⁹). This would indicate a lower rate of oxidation of dextrose together with that of the ingested fat in the obese persons.

On the other hand, there is some evidence of an increased stability of the fat deposits in obese persons as compared with those in normal persons. The fat stored in the adipose tissue in the former is not mobilized and made available for the organism so readily in case of need. My former collaborators Paschkis and Buttu³⁰ found that prolonged hyperventilation, as well as the oral ingestion of large amounts of alkali, both of which produce an alkalosis, raises the level of ketone bodies in the blood of normal persons, but that they are almost or entirely without this effect in obese persons. A ketonemia produced in such a manner is due to mobilization of fat deposits, which apparently, under the circumstances cited, does not take place so readily in obese as in normal persons. Under normal conditions creatinuria following glycogen mobilization in striated muscles, as in hunger, general anesthesia or various infections, is associated, according to Brentano, with a spontaneous endogenous rise of ketone bodies in the blood due to a mobilization of the fat deposits. Some obese persons, however, fail to react with a rise of ketone bodies in the blood during increased

28 Medvei, C. V. Untersuchungen über den Kohlehydratstoffwechsel der Fettsüchtigen, Blutmilchsaure und Blutzucker bei der Arbeit, *Ztschr. f. klin. Med.* **122** 607, 1932.

29 Lauter, S., and Neuenschwander-Lemmer, N. Ueber den Ketonkörpergehalt des Blutes bei Fettsüchtigen und Normalen, *Ztschr. f. d. ges. exper. Med.* **99** 745, 1936.

30 Paschkis, K., and Buttu, G. D. Untersuchungen über die Hyperketonämie bei Hyperventilation und anderen alkalotischen Zuständen, *Ztschr. f. klin. Med.* **123** 764, 1933, Ueber die Ketonkörperbildung beim Fettsüchtigen (Beitrag zur Pathologie des intermediären Stoffwechsels bei der Fettsucht), *ibid.* **123** 776 1933.

creatinuria (Brentano²⁷) MacKay and Sherrill³¹ studied the ketonuria exhibited during a fasting period by both obese and normal persons. One group of the obese persons whose conditions were classified as endocrinopathies, but which I should call rather endogenous types of obesity, excreted appreciably less ketone bodies than normal persons. In the other group whose obesity was classified as "simple"—apparently of the "exogenous" variety—the ketonuria was as great as, and usually even greater than, in normal persons. MacKay and Sherrill concluded that the first group had some sort of "locked fat." In my own experience, obese persons do not exhibit ketonuria so readily as normal persons if put on a diet poor in carbohydrate.

Hetenyi³² reported experiments on obese subjects showing a markedly lower rise of the lipid level in the blood as compared with normal subjects if large amounts of fat were administered by mouth or subcutaneously or if artificial fever was produced. Even Wilder,^{5b} who had been rather skeptical in 1932, stated in 1938, in commenting on these studies of Hetenyi:

These observations seem to indicate that mobilization of fat from fat depots is resisted in obesity and that deposition is accelerated. The condition seems analogous to the increased stability of deposits of glycogen in the liver and in the muscle in von Gierke's disease (glycogenosis). It seems to me that this conception deserves attentive consideration.

This conception is exactly the same as that which I⁴ pronounced in 1929:

Like a malignant tumor or like the fetus, the uterus or the breasts of a pregnant woman, the abnormal lipophilic tissue seizes on foodstuffs, even in the case of undernutrition. It maintains its stock, and may increase it independent of the requirements of the organism. A sort of anarchy exists, the adipose tissue lives for itself and does not fit into the precisely regulated management of the whole organism.

If I may put it somewhat exaggeratedly. A lipomatous subject may die of starvation and still remain lipomatous.

Finally, I want to mention that my former collaborator dell'Acqua³³ studied the amount of lipase present in the adipose tissue obtained from the living person during a surgical operation. The lipase content of the adipose tissue was found to be lower in obese than in normal persons and was lowest in the tissue of true lipomas.

31 MacKay, E. M., and Sherrill, J. W. A Comparison of the Ketosis Developed During Fasting by Obese Patients and Normal Subjects, *Endocrinology* **21** 677, 1937.

32 Hetenyi, G. Untersuchungen über die Entstehung der Fettsucht, *Deutsches Arch f klin Med* **179** 134, 1936.

33 dell'Acqua, G. Ueber den Lipasegehalt des Fettgewebes bei Fettsucht und Lipom, *Ztschr f d ges exper Med* **71** 245, 1930.

From the foregoing statements it is evident that such an increased lipophilia is associated with an increased hydrophilia, that is, with an increased tendency to retain water and salt. This holds whether the abnormality is limited to particular regions of the body or is more or less generalized. An abnormally high hydrophilia may easily be tested and used as an indicator for an abnormally high lipophilia. This statement is of great practical value. Reduction of salt and fluid in the treatment of obesity is an essential point in my opinion, as in that of every one who has any experience in treating obese persons. It counteracts the manifestation of hydrophilia and, as it seems, therewith also that of lipophilia. In complete accordance with this view, Wohl³² emphasized the importance of therapeutic dehydration, because thereby an obese subject "not only loses weight but is prevented from accumulating fat"³⁴

It is conceivable that an abnormal "hydrolipophilia" may represent the primary disturbance resulting in an increased appetite and a subsequent imbalance between food intake and energy output, with a diminished specific dynamic action of food and even a lowering of the basal metabolic rate. It is the distribution of energy, too, that counts, not alone the rough imbalance between its intake and output.

It is erroneous to consider the adipose tissue merely as a passive storing place for fat and not to recognize that the adipose tissue as a part of the living body has, too, its own physiologic and pathologic processes.

What are the factors determining and influencing the lipophilia of the subcutaneous tissue? Three such factors must be assumed: an autonomous, an endocrine and a nervous.

(a) *The Autonomous Factor* From the aforementioned facts, particularly from the results of skin grafts transplanted from the abdominal wall to the back of the hand, it is evident that any particular region of the skin has its own autonomous lipophilia which is a hereditary trait and characteristic of the particular region.³⁵ Physicians who are accustomed to study not only the patient but also his family will notice that identical or similar varieties of female fat distribution are found in other members of the family. The different varieties of fat distribution in women characterize the strain, they represent a hereditary, that is, a constitutional trait. Any such constitutional trait may, under certain

34 Best and Taylor,¹ in their excellent textbook, stated (page 982) "Undue restriction of the water intake is sometimes practised but this appears to be of no benefit and may be a detriment to health." Such a statement of physiologists is certainly not based on personal experience. In some fields clinicians have to teach the physiologists, and not, as usual, the contrary!

35 Bauer, J. (a) Individual Constitution and Endocrine Glands. *Endocrinology* 8: 297, 1924, (b) footnote 15.

circumstances, become not only a familial but also a racial characteristic. The best example is what is called steatopygia in Bushmen, Hottentots and certain strains of sheep. The local accumulation of huge masses of adipose tissue in the buttocks represents an obvious racial characteristic. Sexual selection in man and artificial breeders' selection in sheep have transformed a formerly constitutional into a racial trait.

Hoffmann and Weirheimer⁹ fed chiefly carbohydrates to dogs which had lost most of their fat during a previous period of starvation. They found an accumulation of glycogen in the adipose tissue, indicating the increasing storage of fat. Yet the glycogen was not equally distributed in all parts of the adipose tissue, but was found only in those places in which an actual accumulation of fat took place. In the adipose tissue of the orbits and of the soles, which remains practically unchanged during both starvation and fattening, no glycogen deposits could be observed. This experiment throws an interesting light on the autonomous regional differences of lipophilia, as well as on its biochemical nature.

(b) *The Endocrine Factor.* The most obvious influence on the regional lipophilia of the subcutaneous tissue is exerted by the testicles. The testicular hormone inhibits the accumulation of adipose tissue in those parts of the body which represent the chief sites for the accumulation in normal women, such as on the lower part of the abdomen, around the hips, at the breasts and thighs and on the back, where characteristic wide transversal folds of adipose tissue are found in the lateral parts. If the testicular hormone is lacking, the tendency toward accumulation of fat becomes obvious in those parts in which it is checked under normal conditions. Hence the female, or eunuchoid, type of distribution of adipose tissue occurs in castrated men or in those whose testicles have been destroyed by pathologic processes or have undergone atrophy on account of a primary lesion of the anterior lobe of the pituitary gland or of a definite hypothalamic center, or whose testicles were primarily hypoplastic and did not grow at the age of puberty ("eunuchoidism"). Hence, also, the regular female, or eunuchoid, type of fat distribution is present in obese boys in whom the physiologic production of the testicular hormone is not yet sufficient to prevent the accumulation of adipose tissue of the female type. The larger the quantity of fat deposited, the more striking is the resemblance to the female type and the more likely it may be erroneously considered as a sign of Frohlich's dystrophia adiposogenitalis. This variety of prepubertal fat distribution might well be termed also the asexual, or sexually undifferentiated, type, since it is independent of sex hormones and is equally common in both sexes. Its presence at the prepubertal age by no means justifies the assumption of a gonadal or pituitary insufficiency.³⁶

36 Bauer, J. Common Diagnostic and Therapeutic Errors in the Management of Fat Boys, *M. Rec.* **151** 89, 1940, footnote 35a.

The ovaries have no influence on the regional distribution of adipose tissue^{35a}. Castrated women do not differ from normal ones as far as the distribution of adipose tissue is concerned. What is frequently described as the hypogonadal variety of fat distribution, that is, the trochanteric deposit of fat pads, has no causal connection whatsoever with hypogonadism. Such a statement never has been substantiated and is simply copied by one author from another.

On the other hand, it cannot be denied, although hardly proved that an insufficiency or absence of ovarian function may increase the general lipophilia under certain conditions. The mere energy concept cannot account for the obesity which develops immediately after castration or after the onset of any type of ovarian insufficiency. As a matter of fact, in only a moderate percentage of patients with such insufficiency does obesity actually develop. The ovaries have an influence on the hydrophilia, however. At the beginning of the menstrual period a tendency to retention of water and salt is found in normal women (Heilig⁹). During this time obese women gain in weight or do not respond to the dietetic restriction as they do before and after menstruation.

Insulin has been shown to enhance the deposition of carbohydrates in the adipose tissue (Hoffmann and Wertheimer⁹, Loew and Kičma²³, Richter²⁴, Scoz, Baer and Boeri²⁵). This fact throws light on the nature of lipophilia and on the importance of considering the distribution of energy rather than merely the rough balance between intake and output. It is the intermediary metabolism which determines this distribution, and it is the intermediary metabolism which is obviously somewhat different in obese and in normal people. One part of the fattening effect of insulin injections on thin persons is to be attributed to the increased lipophilia of the adipose tissue.

The adrenal cortex has an influence on the lipophilia. The adiposity which occurs, together with other symptoms and signs, in cases of tumors of the adrenal cortex can by no means be explained by a simple imbalance between intake and output of energy, all the more if the characteristic accumulation of the adipose tissue in the face, the neck, the back and the upper part of the abdomen in contrast to the slender extremities is considered. It is a somewhat male type of fat distribution which is brought about in female persons with adrenal cortical tumors.

The pituitary gland has an indirect influence on lipophilia through the intermediation of both gonadal atrophy, in Frohlich's syndrome, and adrenal cortical hyperactivity, in Cushing's syndrome³⁷. It is, however, questionable whether or not the pituitary gland may influence directly

37 Bauer, J. Was ist Cushing'sche Krankheit? Schweiz. med. Wchnschr. 66 938, 1936.

the lipophilia of the tissues, as one is justified in doubting the existence of a pituitary type of obesity. Yet if obesity should prove to be caused directly by a functional alteration of the pituitary gland, then, again, only an altered lipophilia, and not merely an altered balance between energy intake and output, could account for its pathogenesis.

It may seem strange to doubt whether a pituitary type of obesity exists at all, when the textbooks and papers of clinical endocrinologists state it to be extremely common and correlate the girdle type of fat distribution with the pituitary origin of adiposity. Nobody has ever given a proof of the correctness of this view. The reason for such an erroneous conception is this. The great majority of women exhibit the girdle type of fat distribution, and the obesity of most of them cannot be proved to be of thyroid, gonadal or adrenal origin. As the authors do not realize any other possibility of explaining the nature of such obviously endogenous types of obesity, they make the diagnosis of pituitary obesity by exclusion without any positive evidence of an alteration of the pituitary gland. The more specialized in endocrinology a clinical writer is, the more dogmatic are usually his statements, and these are transmitted from one textbook or paper to generations of following ones.

(c) *The Nervous Factor*. The nerve supply of adipose tissue seems to regulate its lipophilia. If a peripheral nerve is severed or if other lesions of the peripheral nerves or of the spinal cord exist, an increased deposit of fat may result in those parts of the adipose tissue which get their nerve supply from the injured nerve tissue. Hausberger and Gujot³⁸ denervated the interscapular pad of brown adipose tissue in mice and rats and found that it rapidly increased in weight by accumulation of carbohydrate and fat. The brown adipose tissue was almost entirely transformed into the usual white or yellow adipose tissue, as the protoplasm of the cells was replaced by fat droplets. This statement has been amply confirmed.³⁹ In my medical department in Vienna, Adler-

38 Hausberger, F. X. Ueber die nervöse Regulation des Fettstoffwechsels, *Klin Wchnschr* **14** 77, 1935. Hausberger, F. X., and Gujot, O. Ueber die Veränderungen in Fett-, Wasser-, Glykogen- und Trockensubstanzgehalt im entnervten Fettgewebe, *Arch f exper Path u Pharmakol* **187** 655, 1937.

39 Cedrangolo, F. Azione del sistema nervoso sul metabolismo dei lipidi di riserva, *Arch di sc biol* **21** 570, 1935. Beznak, A., and Hasch, Z. Effect of Sympathectomy on Fatty Deposit in Connective Tissue, *Quart J Exper Physiol* **27** 1, 1937. Kure, K., Oi, T., and Okinaka, S. Beziehungen des Spinal-Parasympathicus zu der trophischen Innervation des Fettgewebes, *Klin Wchnschr* **16** 1789, 1937. Bargi, L., and Politzer, M. L'azione del ormone tiroideo sulla struttura istologica e chimica del tessuto adiposo innervato ed enervato, *Rassegna di fisiopat clin e terap* **9** 613, 1937. Influenza dell'enervezione sulla struttura istologica e chimica del tessuto adiposo, *ibid* **9** 554, 1937.

Monnich and Tiberi⁴⁰ obtained the same results, and unpublished (because incomplete) experiments of Loeb and Hirschfeld seem to reveal a greater content of sodium chloride of the denervated fatty pad than that of the intact side. Diastase has been found in larger amounts on the denervated side (Hausberger⁴¹). Recent experiments seem to indicate that denervation of the intercapsular adipose tissue in white rats is followed by an increased tendency to deposit fat if a fat of a widely different iodine value is administered in large quantity after a period of starvation (Bauer, Nadler and Schwoner⁴²).

These facts point toward an increased lipophilia as the operative factor in cases of so-called cerebral or hypothalamic obesity. Erdheim⁴³ many years ago, came to the conclusion that when tumors of the pituitary gland were associated with obesity (dystrophia adiposogenitalis of Babinski and Frohlich) the obesity was due to compression of certain cerebral centers on the floor of the third ventricle. Camus and Roussy⁴⁴ as well as Bailey and Bremer,⁴⁵ confirmed this view on the basis of their animal experiments. Since epidemics of encephalitis have begun to occur, one occasionally meets with cases in which obesity develops as the result of inflammatory damage to these hypothalamic centers. Syphilitic or postvaccinal encephalitis, rheumatic chorea, tumors of the brain or hydrocephalus may produce obesity through the intermediation of a hypothalamic lesion. I observed extreme obesity develop in a young girl after scarlet fever associated with encephalitis. Definite evidence of the hypothalamic rather than of the pituitary origin of obesity occurring in cases of lesions around the hypophyseal region has been given by the excellent work of Smith⁴⁶. He succeeded in producing extreme adiposity in rats by experimentally injuring the tuber cinereum without involvement of the hypophysis. He failed, however to obtain a similar result by removing or injuring the pituitary gland without involvement of the hypothalamic region.

40 Adler-Monnich, J, and Tiberi, R. Untersuchungen zur Biologie des Fettorgans, Wien Arch f inn Med **30** 259, 1937

41 Hausberger, F X. Ueber die Veränderung des Gehaltes an diastatischem Ferment im entnervten Fettgewebe, Ztschr f d ges exper Med **102** 169, 1937

42 Bauer, J, Nadler, S B, and Schwoner, A M. The Effect of Nervous and Endocrine Influences upon the Fat Deposition in the Subcutaneous Adipose Tissue, to be published

43 Erdheim, J. Ueber Hypophysengangsgeschwulste und Hirncholesteatome Sitzungsber d k Akad d Wissensch Math-naturw Cl (pt 3) **113** 537, 1904

44 Camus, J, and Roussy, G. Experimental Researches on the Pituitary Body, Endocrinology **4** 507, 1920

45 Bailey, P, and Bremer, F. Experimental Diabetes Insipidus, Arch Int Med **28**:773 (Dec) 1921

46 Smith, P E. Disabilities Caused by Hypophysectomy and Their Repair. Tuberal (Hypothalamic) Syndrome in Rat, J A M A **88** 158 (Jan 15) 1927. Hypophysectomy and Replacement Therapy in Rat, Am J Anat **45** 205, 1930

Regarding the aforementioned facts, it seems justified to refer to an increased lipophilia of the adipose tissue as the chief cause of such a cerebral obesity. At all events, such a conception is better substantiated and more satisfactory than Wilder's⁵ hypothesis explaining cerebral obesity by an abnormal irritability of centers of the diencephalon, where feelings of hunger and satiety originate. As I pointed out previously, these general feelings are adapted to the quantitative (energy) and qualitative requirements of the organism, they are under normal conditions, of course, ruled by this requirement.

2 Definition of Obesity—I purposely did not try to give a definition of what may be called obesity until I had discussed the complicated matters leading to a better comprehension of the problem. I mentioned the difference between obesity and temporary overweight brought about by an induced imbalance between food intake and energy output. The German language permits a fine distinction between *Fettleibigkeit* and *Fettsucht*. The former defines an actual state of overweight, so to speak, a static condition of what may be called an excessive corpulence, the latter characterizes a dynamic tendency toward overweight. That is what I want to call obesity. Obesity may be defined as the compulsory tendency toward marked overweight due to abnormal accumulation of fat by persons who are left alone to their automatic regulations and are not supervised as far as the intake of food and expenditure of energy are concerned. The more localized such an abnormal accumulation of fat is, the more it is justified to call it lipomatosis rather than obesity. Yet there are no sharp limits between lipomatosis and obesity, as well as between obesity and the particularities of a lateral (pyknic) habitus which may still be considered normal. What has recently been described as "lipedema of the legs—a syndrome characterized by fat legs and orthostatic edema" (Allen and Hines⁴⁷) is merely a not uncommon variety of such a hydrolipomatosis, which has been well known and studied for many years.⁴⁸

Only the definition of obesity as I have given it suits the generally accepted conception of experienced clinicians who include obesity among metabolic diseases. Were obesity merely the result of a simple imbalance between intake and output of energy, it would not be justified to call it a metabolic disease. Corpulence of temporary character brought about by artificial overfeeding or artificial restriction of muscular exercise is not a metabolic disease.

47 Allen, E. V., and Hines, E. A. Lipedema of the Legs. A Syndrome Characterized by Fat Legs and Orthostatic Edema, Proc. Staff Meet., Mayo Clin. **15** 184, 1940.

48 Bauer, J. (a) Innere Sekretion, Berlin, Julius Springer, 1927, (b) Die Behandlung der Fettsucht, Klin. Wchnschr. **9** 2161, 1930.

3 *Etiologic Factors in Obesity*—As I pointed out, there is no such thing as pure exogenous obesity. All obese patients must have at least a certain individual predisposition, that is, they must have a weight-regulating mechanism which is more readily overthrown than a normal one. All obesity is to a variable extent endogenous.

(a) *Endocrine Obesity*. There are cases in which obesity develops as a result of a tumor or other pathologic process in one of the endocrine glands. These cases justify the classification of hypothyroid, hypogonadal, adrenal and pituitary obesity. It is, however, a very small number of cases of obesity in which the condition may be classified as endocrine with full right. A critical analysis is necessary in order to declare an endocrine disturbance as the actual cause of obesity in a particular case.

Castrates and eunuchoids may be tall and slender as well as obese.⁴⁹ After the menopause only a moderate number of women, about 20 to 30 per cent, increase in weight. Estrogen or progesterone therapy has practically no influence on obesity. On the other hand, dietetic reduction of body weight without hormonal therapy may regulate a menstrual disorder. This experience has also been had by Wilder⁵ and by Evans.⁵⁰

Irregularity of the rhythm or intensity of menstruation, a late or premature onset or cessation of the menses, sterility, abnormality of the growth of hair, the presence of ovarian cysts and uterine fibromas, some diffuse or nodular enlargement of the thyroid and many other signs of abnormal endocrine function do not, in the majority of cases of obesity, indicate the cause of obesity but represent what I have called "endocrine stigmatization."⁵¹ Obesity may have been present from early childhood, long before the abnormality of the ovarian function occurred. Hypertrichosis may persist unchanged after puberty and may be present in other members of the family who are not obese. The enlargement of the thyroid may not show any temporal connection with the onset of obesity and may not be associated with any functional disorder of the gland. Such an endocrine stigmatization therefore merely indicates some deviation in the glandular structure or activity and does not supply a sufficient explanation for a special glandular origin of the obesity.

(b) *Cerebral Obesity*. This variety is even rarer than endocrine obesity if diagnosis is based on undeniable facts, that is, on the evidence

49 Not all animal species gain in weight after castration.

50 Evans, F. A. *Nature of Obesity in Endocrine Disorders*, Pennsylvania M. J. **42** 1174, 1939.

51 Bauer, J. *Die endokrinen Stigmatisierten*, Deutsche med. Wchnschr. **58**: 439, 1932, footnote 48a.

of a cerebral lesion being the cause of obesity in a particular case. In an analysis of 275 unselected cases of high grade obesity which I⁴ published twelve years ago, there were only 2 instances of cerebral and 5 of endocrine adiposity. In all the rest of the 268 cases such a diagnosis could not be made.

(c) Constitutional Obesity. The term "constitutional" indicates any condition which is determined by the germ plasm, that is, any trait, either normal or pathologic, which is due to a particular gene or mendelian unit and is therefore hereditary. In the analysis of 275 cases, 73 per cent were found in which one or both of a patient's parents were obese too. If members of the family other than the parents were included, a hereditary factor was suggested in 88 per cent of the cases. These figures can be approximately confirmed from a material of at least 1,000 cases. The figures are significant even in full consideration of the great frequency of obesity. According to Carey,⁵² it has been estimated that 1 of every 5 adults in the United States is overweight. Some authorities, for example, the physiologists Best and Taylor,¹ have claimed that the role of heredity in obesity is more apparent than real. Any experienced physician with open eyes knows that such a heredity cannot but be real (Wilder,⁵ Gurney⁵³). As a matter of fact, the constitutional character of the obesity in a particular case cannot be ruled out even if no other members of a patient's family can be found to be obese. This follows from the laws of heredity. I wish to stress the fact that in families affected with the hereditary trait of obesity, the condition is not exhibited by all members of the family. If, in spite of the same educational influence and the same environment, obesity develops in some members of a family and not in others, this is in full accordance with the laws of heredity. It does not, however, support the theory that particular habits arising from environment and education may account for an imbalance between food intake and energy output.

If any one were still in doubt whether or not obesity is really inherited, he would be convinced by the following two observations. Christiansen⁵⁴ described a family in which 2 sisters had 5 children each. Three and four, respectively, of the two sets of 5 children were rather big at birth. These babies, immediately after birth, displayed extraordinary appetites, grew very rapidly and accumulated prodigious amounts of fat. Only 1 of them survived the first year. Autopsy, performed in 1 case, did not reveal any explanation of the peculiar "macrosomia adiposa congenita," as the author termed the condition. This observation demon-

52 Carey, L. S. Obesity, *M. Clin. North America* **23** 1449, 1939.

53 Gurney, R. The Hereditary Factor in Obesity, *Arch. Int. Med.* **57** 557 (March) 1936.

54 Christiansen, T. Macrosomia Adiposa Congenita. New Dysendocrine Syndrome of Familial Occurrence, *Endocrinology* **13** 149, 1929.

strated again that overfeeding is clearly not the real cause but rather the compulsory consequence, of the pathologic anlage for obesity. Overfeeding is nothing but the means for the realization of the potentialities of this anlage.

Danforth⁵⁵ bred a strain of yellow mice presenting extreme obesity as a hereditary, dominant mendelian characteristic. Neither macroscopic nor microscopic examination revealed any abnormality to explain it. It is particularly interesting, in relation to Christiansen's observation, to note that in Danforth's strain of mice the pathologic anlage for obesity proved to be a so-called lethal factor if it was inherited from both parents; that is, if the mouse was a homozygote in respect to the character.

How does heredity operate to bring about obesity? Which anatomic structures or which functions does the hereditary factor affect? From the previous discussion it is clear that the gene or genes producing obesity do not affect one particular part of the body only, such as the thyroid, the pituitary or other endocrine gland, or some brain center which governs the accumulation of fat or is responsible for the general feelings regulating the balance of energy introduced into and spent by the body.

Without doubt the hereditary factor affects the local lipophilia of the tissues. This is proved by the previously mentioned familial type of regional accumulation of adipose tissue. I recall once more the *steatopygia*, which is a racial characteristic.

In addition, however, the anlage for obesity seems to operate also through the endocrine glands regulating the lipophilia and the metabolic conditions of the body. Such an assumption does not indicate a particular structural abnormality, an actual disease of one or several glands; it merely points to some functional alteration of the glands cooperating in the production of obesity. This is suggested by the frequent disturbance of various endocrine functions in obese persons and in members of their families. I discussed this fact previously and concluded that such an endocrine stigmatization is not to be looked on as the pathogenetic factor of obesity. It merely indicates some sort of biologic inferiority of the endocrine system.

It is not only a harmless state of endocrine stigmatization, however, which is met with in obese families. It is not exceptional to find a more serious alteration of some gland, such as a tumor, hypoplasia or atrophy, as the result of the biologic inferiority. I know several families in which constitutional obesity is present and in certain members of which tumors of the pituitary gland have developed at an advanced age. In these persons the obesity is not the result of the tumor; it is undoubtedly constitutional and has dated from early childhood. I also know obese families in which the members are obese, one of whom is a eunuchoid.

⁵⁵ Danforth, C. H. Hereditary Adiposity in Mice. *J. Heredity* **18**: 153, 1927.

In such a case the vicious cycle is obvious. The inherited constitutional obesity is the real cause of the biologic inferiority of the glandular system, and one of the glands became the particular victim of such an inferiority. Hypoplastic testicles may produce on their part the characteristic type of fat distribution and accumulation which is called eunuchoid obesity. In other words, a person with eunuchoid obesity may not be obese because of his gonadal hypoplasia but may display eunuchoidism as a result of a repercussion of the anlage for obesity on his gonads.

It fits well in the general pattern of the activities of genes and their relation to the phenotype if it is assumed that the genes causing obesity exert their influence not only on the local lipophilia of the adipose tissue but also on the endocrine glands and those centers of the central nervous system which regulate lipophilia and dominate metabolic functions, as well as those which are the site of the general feelings ruling the intake of food and the expenditure of energy. The analysis of the relations between the structure of the genotype and that of the phenotype is, in my opinion, the main task of constitutional physiology and pathology. The way in which the marvelous potential energies, represented by the genes and located in the chromosomes, bring about and rule the harmonic system of organs and functions of the living organism must be the chief objective of studies in the field of constitutional physiology and pathology. No matter whether or not this conception is entirely correct, one thing has to be kept in mind. It is that the definite body weight, the amount of adipose tissue deposited in the body, is determined by the germ plasm. The mass of the body as well as its height is determined by genes. All structures and functions involved in producing the mass and the height of the body seem to depend in some way on these genes.

4 *The Relations of Obesity to Other Constitutional Abnormalities* —

In considering an abnormal gene or gene complex as the cause of constitutional obesity, one must ask whether or not something is known about other genes related to the obesity anlage. First a negative statement can be made. The four blood groups have no relation to obesity.

Yet the hereditary factor which produces obesity may be associated with other abnormal hereditary characteristics and may represent in this way only one part of a more complicated abnormal constitutional syndrome. What has been described and discussed rather frequently in the last few years under the name of the Laurence-Moon-Bardet-Biedl syndrome is an association of obesity with polydactylism and syndactylism, retinitis pigmentosa, hypogenitalism, abnormalities of the skull (usually oxycephaly), deficient intelligence and occasionally other degenerative stigmas. Not all of the symptoms are met with in all cases, and a dissociation may be occasionally found in several members of one family.

I⁵⁶ have pointed out, as have my former collaborators Aschner⁵⁷ and Pool,⁵⁸ that the only satisfactory explanation of this peculiar syndrome is an alteration of several hereditary factors probably associated with each other by linkage of genes. This is a term used by geneticists for a persistent association of genes localized in the same chromosome, and therefore exposed more readily to a common alteration.

In a case under my own observation which was reported by Pool, extreme familial obesity in a 12 year old girl was associated with polydactylism, syndactylism, hypophalangism due to an abnormal fusion of the phalanges, a marked congenital deformation of the skull to be classified as acrocephaly, and intellectual disorders. This case represents a combination of two constitutional syndromes, the Bardet-Biedl and the Apcrt syndrome, which is called "acrocephalosyndactylism." At birth the girl had a weight of 6 Kg (13.2 pounds). This fact justifies consideration of the adiposity as constitutional. It fits into Christensen's⁵⁴ "macrosomia adiposa congenita." At the age of 12 years the weight was 182 Kg (400 pounds) and the height 157 cm. Two brothers of the mother had a body weight of 160 Kg (352 pounds) each; a third weighed 110 Kg (242 pounds).

Another syndrome in which obesity is the leading symptom is the so-called Morgagni syndrome, which is characterized by the combination of obesity with a peculiar hyperostosis frontalis localized on the inner surface of the frontal bone and by some signs of virilism, such as hypertrichosis in women (Henschen⁵⁹). I cannot agree with those authors who try to explain this syndrome as a pituitary or pluriglandular disorder. An association of several abnormal genes seems far more probable, in my opinion, as I have occasionally met frontal hyperostosis as a constitutional abnormality without any other pathologic condition. In some cases frank imbecility or psychoneurotic symptoms are associated with this syndrome, and rudimentary, as well as full blown, forms may be associated with an atypical set of symptoms belonging to the Bardet as well as to the Morgagni syndrome. This is in complete accord

56 Bauer, J. Problems of Human Genetics, Bull. Johns Hopkins Hosp. **44**: 52, 1929, Constitutional Principles in Clinical Medicine, in Harvey Lectures, 1932-1933, Baltimore, Williams & Wilkins Company, 1934, footnotes 4 and 48a.

57 Aschner, B. Zur Erbbiologie des Skelettsystems. Beiträge zur Humänen Konstitutionspathologie, Ztschr. f. d. ges. Anat. (pt. 1) **14**: 129, 1928, Ueber die Arbeitsmethoden der menschlichen Erbforschung, Wien Klin. Wchnschr. **49**: 1704, 1333 and 1362, 1936.

58 Pool, F. L. Zur Entstehung genopathischer Syndrome (Bardet-Biedl-Akrocephalo-Syndaktylie), Wien Arch. f. inn. Med. **31**: 187, 1937.

59 Henschen, F. Morgagnis Syndrom, Hyperostosis frontalis interna, Virilismus, Obesitas, in Aschoff, L., Ceelen, W., Koch, W., and Scharmann, P. Veröffentlichungen aus der Konstitutions- und Wehrpathologie, Jena, G. Fischer, 1937, vol. 9, pt. 2.

with my explanation Van Bogaert and Borremans⁶⁰ described a family whose members were affected with obesity, retinitis pigmentosa, brachydactylism and frontal hyperostosis. The irregular but frequent association of obesity with many different signs of a deviating constitution puts obesity among the other signs of what I have called "status degenerativus"⁶¹. The term indicates an accumulation of many signs of a deviating, and therefore abnormal, constitution in one person.

In this same connection must be recalled the not infrequent association of obesity and biliary concretions, arteriosclerosis, diabetes and arterial hypertension. In the last two conditions the relationship to obesity is probably more intimate than one based merely on a common abnormal degenerative constitution. Hyperglycemia in obese persons frequently disappears after proper reduction of weight (Labbé⁹), and marked arterial hypertension in obese persons may be considerably lowered if the weight is reduced (Aschner⁶²). Those are facts of great practical importance.

TREATMENT OF CONSTITUTIONAL OBESITY

Since as physicians we are unable to alter hereditary factors, it might seem that effective treatment of such an inherited constitutional condition as obesity would be impossible. Mendelian factors represent the unchangeable fate of a person, it is true, but we are still able to do a great deal for those whose inherited tendencies lead them to undesirable conditions. We may change the environment indispensable to the realization of the potentialities of the genes, and we may counteract their activity by interfering with the mechanism of the realization.

Many constitutional abnormalities exist which can be practically cured in spite of the impossibility of changing the underlying genes. Surgical procedures can repair polydactylism or syndactylism, a cleft palate and similar abnormalities. If a woman with black hair wishes to change this constitutional characteristic, she merely dyes it. On the other hand, she has to continue to dye it all her life if she wishes to hide it permanently, and the same reasoning holds true for the suppression of the anlage for obesity.

A normal person regulates his intake and output of energy automatically because of such general feelings as appetite and satiety and

60 van Bogaert, L, and Borremans, P. La forme familiale de la retinite pigmentaire avec cécité et obésité dite cérébrale (première observation anatomique), *Ann de med* **39** 54, 1936.

61 Bauer, J. Vorlesungen über allgemeine Konstitutions- und Vererbungslehre, ed 2, Berlin, Julius Springer, 1923, Konstitutionelle Disposition zu inneren Krankheiten, ed 3, *ibid*, 1924.

62 Aschner, B. Beziehungen der Fettsucht zu arteriellem Hochdruck, Diabetes mellitus und Cholelithiasis, *Ztschr f klin Med* **116** 669, 1931.

because of his normal glandular and nervous functions. A person with a constitutional obesity which he wishes to suppress cannot rely on his automatic regulations and must follow a certain regimen which counteracts them. In other words, the obese person is forced to eat and drink not what he wants but what his physicians consider useful. He cannot rely on his automatic regulations if he wishes to avoid the consequences of his constitutional trait. We are fully aware of the fact that our treatment of obesity cannot be entirely satisfactory so long as we are not familiar with all the abnormalities of the pathologic intermediate metabolism and so long as we have no possible way of influencing the abnormal lipophilia of the fat-accumulating tissue. We can, however, inhibit the abnormal tendency by a number of means.

In no case should obesity be treated without the prescription, first of all, of a dietetic regimen. All other therapeutic procedures are secondary to this one. Not only a general quantitative reduction of calories should be instituted, but their quality should also be considered. Carbohydrates and fat are known to be likely to be deposited as fat, whereas proteins are more readily burned and utilized. They stimulate the thyroid activity and have the greatest specific dynamic action. This sort of fuel increases the flame in the stove more than any other variety.

On the basis of these facts, we put the patient on a diet containing about 1,100 calories, but no more than 20 to 30 Gm. of fat and 85 Gm. of carbohydrate. The rest of the diet consists of such proteins as lean meat, fish, cheese and eggs. I have sometimes had the rather paradoxical experience that patients whose general intake had been increased by the addition of protein calories lost in weight, whereas their former diet, although poorer in total calories, did not have this effect. Proteins in not too small amounts are indispensable in any case in which the body weight is to be reduced, in order to prevent the risk of damage to parenchymatous organs from chronic undernourishment.

It is necessary, too, to restrict the intake of salt to about 2 to 3 Gm. per day and to limit as far as possible the intake of fluids of all kinds. By this treatment alone all obese patients lose up to a certain point. There the weight becomes stationary, partly as the result of water retention.

At this stage thyroid should be given if no contraindication, such as marked tachycardia, cardiac insufficiency or a definite hyperthyroid state, prevents its use. It should be given regardless of the presence or absence of hypothyroid symptoms. It must act here not as a substitute for insufficient thyroid function but as a stimulant for the oxidative processes and the mobilization of water and salt from the tissues. The basal metabolic rate is of little or no value in deciding whether or not thyroid should be given. The general clinical picture, however, is decisive.

The duration and degree of thyroid treatment depend on the tolerance and reaction of the patient. Relatively high doses are advisable for four to six days, and the "thyroid push" should be repeated after several days of rest. This method seems more effective than the administration of small doses of thyroid continuously over long periods.

It is well known that many obese patients react to relatively mild thyroid treatment with tachycardia and increased nervous irritability, so that this therapy must be discontinued before the desired loss in weight has been produced. In such cases small, nontoxic doses of thyroid should be given in combination with intramuscular injections of a protein preparation. The simplest method is the injection of from 3 to 5 or 8 cc of boiled milk every four to six days. Neither the thyroid nor the protein therapy in itself decreases the body weight, only the combination is effective. It seems that the protein injections determine the direction of the thyroid activity toward the metabolic processes, these being sensitized by the parenterally administered protein.

When the tendency to water retention is obvious, particularly if it is increasing, the use of a diuretic containing mercury, such as salyrgan or merbaphen, is indicated. The administration of the diuretic should be repeated as necessary at intervals of at least four to six days, and the effect can be markedly increased by the production of artificial acidosis through the oral administration of ammonium chloride, in doses of from 4 to 8 Gm per day, for two or three days before and on the day of the injection of the mercury-containing diuretic. In many cases a "water push," that is, the intake of 1,000 to 1,500 cc of water within fifteen to thirty minutes, may have the same dehydrating effect as the use of a diuretic. In spite of the delayed elimination of the liquid in hydrophilic obese persons, the exaggerated, though delayed, diuresis and the extra-renal loss of water may produce a considerable loss of weight after twenty-four to forty-eight hours. This method has been described by my former associate Aschner⁶³. A similar underlying principle is employed in various spas in which saline waters are used to promote intestinal and renal elimination of water.

The output of energy should be increased as far as possible by the prescription of greater muscular activity, in the form of walking and other physical exercises, with due regard to the patient's cardiac state. Massage is indicated to loosen fatty masses, particularly when they are accumulated in certain regions of the body surface. This is the only, and unfortunately not a very satisfactory, way to determine the sites in which mobilization of fat should take place. Patients with hydro-lipomatous legs should wear elastic stockings to prevent the accumulation of water. When huge masses of fat have accumulated, particularly in

63 Aschner, B. Zur Therapie der Fettsucht, *Klin. Wchnschr.* 7 2242, 1928

the lower part of the abdomen, their surgical removal may sometimes be of great value, though surgical intervention should always be preceded and followed by appropriate general treatment

The question whether glandular preparations other than thyroid should be used in the treatment of obesity is still widely discussed. My personal experience leads me to say that only estrogen preparations need be taken into consideration, and then only when ovarian insufficiency is clear. They may diminish the tendency toward water retention to a certain extent. They may aid in provoking menstruation when amenorrhea is present. But they have no effect on the obesity itself. The animal experiments of my former collaborators Adler-Monnich and Tiberi⁶⁴ make it seem advisable not to prescribe thyroid and estrogen preparations at the same time as the effect of the estrogen is checked by the thyroid. I have never seen any improvement in obesity from the use of preparations of the pituitary. The different combinations of glandular substances now available for clinical use are at the best superfluous, such effect as they produce is dependent on the thyroid substance which they contain.

Finally, but not of least importance one point should be stressed. If the reduction in weight has reached a certain point and a further reduction seems impossible, treatment should be discontinued for several weeks, during which time the weight is kept unchanged by an appropriate diet. The resumption of treatment after this period often results in a further reduction of weight.

Once more I should like to emphasize the necessity of maintaining a dietetic regimen for a long period, if not for the patient's lifetime. His general feelings regulating the intake and output of energy eventually seem to adapt themselves to the prescribed regimen so that as a rule, the originally awkward compulsion becomes gradually a habit which is no longer troublesome.

SUMMARY

The current energy theory of obesity which considers only an imbalance between intake of food and expenditure of energy, is unsatisfactory.

It is the distribution of energy in the body too which counts not alone the rough imbalance between its intake and output.

The adipose tissue is not merely a passive storing place for reserve fat, but a living and active part of the body with its own physiologic and pathologic processes.

The tendency of the adipose tissue to accumulate fat (lipophilia) varies widely in different parts of the body and also in different persons.

⁶⁴ Adler-Monnich J, and Tiberi R. Zur Wechselbeziehung zwischen Schilddrüse und weiblichen Geschlechtsorganen, *Wien Arch f inn Med* 32 41, 1938.

Increased lipophilia is as a rule associated with increased hydrophilia (tendency to retain water and salt)

Lipophilia is determined and influenced by (a) an autonomous, (b) an endocrine and (c) a nervous factor

There is some evidence that the adipose tissue of an obese person differs from that of a normal person inasmuch as it has greater lipophilia and resists more a mobilization of fat

Obesity is defined as the compulsory tendency toward a marked overweight due to abnormal accumulation of fat by persons who are left alone to their automatic regulations and are not supervised as far as the intake of food and expenditure of energy are concerned

While obesity is a definite metabolic disease, corpulence of temporary character brought about by artificial overfeeding or artificial restriction of muscular exercise is not

The cause of obesity is in a very small number of cases an endocrine disturbance or an alteration of certain cerebral centers, in the vast majority of cases it is a particular constitution, that is, an abnormal gene or gene complex

An increased appetite with a subsequent imbalance between intake and output of energy is the consequence of the abnormal anlage rather than the cause of obesity

Some more or less typical combinations of the gene for obesity with genes for other abnormal traits are discussed, such as occur in Laurence-Moon-Bardet-Biedl, Apert and Morgagni syndromes

The treatment of obesity is outlined. It must be chiefly dietetic

RIGHT-SIDED AORTA WITH DESCENDING AORTA SIMULATING ANEURYSM

URSULA J ROCHE, M D

ISRAEL STEINBERG, M D

AND

GEORGE P ROBB, M D

NEW YORK

The importance of roentgenography in the diagnosis of congenital cardiac abnormalities has been greatly stressed within the last two decades¹ As a result of this trend, there has been an increase in the percentage of aortic anomalies which have been correctly diagnosed during life However, in spite of routine roentgen studies of the aorta, including esophagrams and roentgenokymograms, the congenital defect is often missed, mainly because the shadow of the aorta cannot be distinguished from the overlying densities of the spine and of the mediastinal structures This difficulty has recently been largely overcome by the use of contrast roentgenograms of the cardiovascular system² The entire aorta, from its origin deep in the cardiac mass, to its final subdivision into the iliac arteries, can now be visualized with this technic³ It is our purpose in this paper to report a case of right-sided aorta which, both by fluoroscopic and by roentgenographic examination, was at first diagnosed as an aneurysm of the aorta Visualization studies, however, excluded aneurysm by revealing the presence of a congenital abnormality of the aorta, and esophageal studies after the establishment of the correct

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From the Department of Therapeutics, New York University College of Medicine, and the Third (New York University) Medical Division of Bellevue Hospital

1 Rosler, H Clinical Roentgenology of the Cardiovascular System, Springfield, Ill, Charles C Thomas, Publisher, 1937

2 Robb, G P, and Steinberg, I Visualization of the Chambers of the Heart, the Pulmonary Circulation and the Great Blood Vessels in Man A Practical Method, Am J Roentgenol **41** 1, 1939, Visualization of the Chambers of the Heart, the Pulmonary Circulation and the Great Blood Vessels in Man Summary of Method and Results, J A M A **114** 474 (Feb 10) 1940

3 Robb, G P, Roche, U J, and Steinberg, I Visualization of the Aorta in Disease, to be published

diagnosis, demonstrated the changes pathognomonic of right-sided aorta which have been described in the literature ⁴

REPORT OF A CASE

T F, a white man aged 50, entered the Third Medical Division of Bellevue Hospital in December 1939 with an acute infection of the upper respiratory tract. He denied having had hemoptysis, thoracic pain, dyspnea or other symptoms of cardiovascular or pulmonary disease. There was no history of syphilis or any previous illness.

Physical Examination—On entry the patient did not appear acutely or chronically ill. The head and the neck showed no abnormalities except a sluggish reaction of the pupils to light. The lungs were clear. The point of maximum intensity of the apical beat was in the fifth intercostal space, 8 cm from the midsternal line, no abnormal pulsations were detected. The heart sounds were normal, the aortic second sound was not accentuated and was greater than the pulmonic second sound. There were no murmurs. The pulse was regular with a rate of 80 per minute. The blood pressure was 118 systolic and 84 diastolic. The abdomen and extremities showed nothing abnormal.

Laboratory Examination—The erythrocyte count was 4,200,000 per cubic millimeter, the hemoglobin content was 88 per cent, the leukocyte count was 9,300, with a normal hemogram, the Wassermann reaction was repeatedly negative, and results of chemical examination of the blood and of urinalysis were within the limits of normal. The conventional electrocardiogram was normal, showing regular sinus rhythm and no deviation of the electrical axis. Stethograms taken over the aortic, pulmonic and apical areas revealed no abnormality. According to the interpretation of a routine teleroentgenogram (fig 1 a) there was a huge saccular dilatation of either the ascending or the descending portion of the aorta. It was suggested that the patient might be a suitable candidate for wiring of the aneurysm, and he was referred to us for visualization studies. Contrast roentgenograms, taken with the patient in the frontal, the lateral and the right and left oblique positions (figs 1 b, 2 and 3), demonstrated conclusively that instead of an aortic aneurysm the patient had a right-sided aorta with striking elongation and tortuosity of the descending portion, which accounted for the bizarre shadow that was mistaken for an aneurysm on ordinary roentgenographic study. After the establishment of the correct diagnosis, esophageal studies (fig 4) made with barium sulfate revealed the pathognomonic inversion of the normal aortic impression on the esophagus.

Conventional Roentgenologic Studies—Fluoroscopic examination and the conventional roentgenogram (fig 1 a) showed that pulmonary fields were clear. There were apparently two leaves to the right half of the diaphragm, the lateral one moving paradoxically with respiration. The size and configuration of the heart in all views appeared to be within the limits of normal for the patient's age and habitus. A semicircular mass extended out from the mediastinum into the right

4 Evans, W. The Course of the Esophagus in Health and in Disease of the Heart and Great Vessels, Medical Research Council, Special Report Series, no 208, London, His Majesty's Stationery Office, 1936.



Fig 1—(a) Conventional teleoroentgenogram, frontal view. The size and the contour of the heart are normal. Note the convex mass along the right side of the mediastinum and the density to the right of the first and second costosternal junctions. The “aortic knob” (white arrow) is small, and the descending aorta is invisible. The left pulmonary artery is unusually prominent.

(b) Contrast teleoroentgenogram, frontal view. The left ventricle and the entire thoracic aorta are opaque. The arrow points to the diverticulum. Note the triangle of decreased density between the right border of the ascending and the left border of the descending aorta. In this and in the following figures, AT indicates the transverse aorta, AD the descending aorta and LV the left ventricle.

pulmonary field from the level of the second to the sixth rib anteriorly. On fluoroscopic examination, this mass was seen to pulsate. Above it, lying at the right side of the superior mediastinum, there was an ill defined density, while on the left side, slightly below the position normally occupied by the aortic knob, there was a small protuberance. Below this, on the left side, no descending aorta could be seen. In the left lateral view (fig 5 *a*) the ascending and transverse portions of the aorta were not well seen, while the descending portion was visualized as it pursued a tortuous course in front of and over the spine.

The right anterior oblique view (fig 4 *b*) showed that the ascending and the transverse portion of the aorta were poorly visualized but that the latter appeared to be behind the trachea, which curved forward at this point. The descending



Fig 2—Contrast roentgenogram, left lateral view (target distance 36 inches [91 cm]). The entire thoracic aorta is filled. The arrow is on the left subclavian artery, pointing down to the diverticulum. In this and the following figures AA indicates the ascending aorta.

aorta could be seen overlying the spine much farther to the right than normally, and there appeared to be a fusiform dilatation in its midportion. This portion showed characteristic aortic pulsations, also demonstrated by roentgenokymograms. The fusiform mass could not be seen in the left anterior oblique projection (fig 5 *b*), and the entire aorta was normal in size. The ascending and the descending limb of the aorta were parallel and in close proximity to each other. The shadow of the aorta in this position looked like a mirror image of the vessel as it is normally seen in the right anterior oblique view.

Esophageal studies in the frontal and right anterior oblique projections (fig 4) revealed that the esophagus was displaced anteriorly and to the left by the arch of the aorta, which made a concave impression on this structure. Immediately

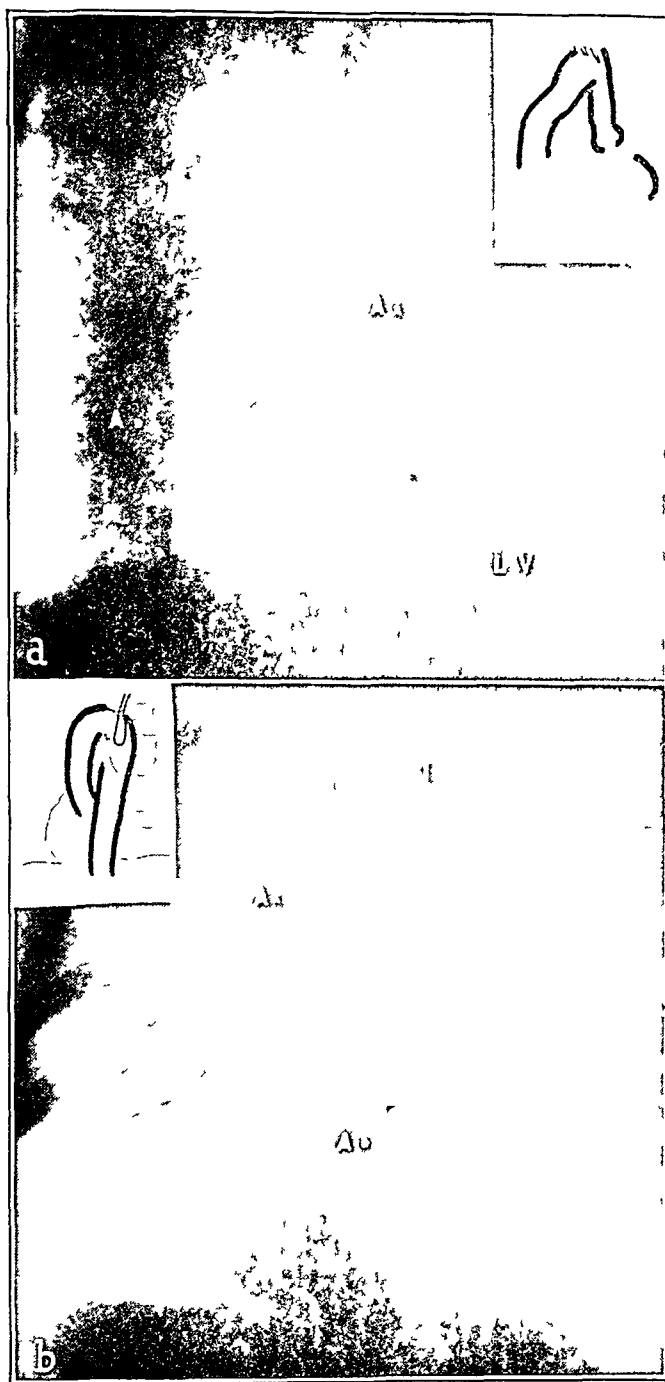


Fig 3—(a) Contrast teleoroentgenogram, right anterior oblique view, at 45 degrees. The left ventricle, the aortic sinus and the entire thoracic aorta are filled. Note the moderate enlargement of the descending aorta and the absence of aneurysm.

(b) Contrast teleoroentgenogram, left anterior oblique view, at 45 degrees. The entire thoracic aorta is filled. The arrow is on the left subclavian artery, pointing to the diverticulum. Note the normal diameter of the ascending aorta and a slight enlargement of the descending aorta.

below this there was a second concavity, while inferiorly the esophagus curved to the right, closely following the course of the convex mass

Contrast Visualization Studies—The course of the aorta within the thorax was reconstructed by the correlation of a series of roentgenograms taken in various projections immediately after the injection of radiopaque material. The aorta, arising at the level of the fifth rib anteriorly, ascended obliquely backward and to the right to the first right costosternal junction, where its "knoblike" appearance was clearly seen, as were the vessels to the neck (figs 1 *b* and 2). It then crossed obliquely downward to the second left costosternal junction, where there was a diverticulum. From this point the aorta curved posteriorly and into the right pulmonary field, describing a large arc, and thence back to the midline near the diaphragm. An end view of the diverticulum, lying immediately behind the trachea,

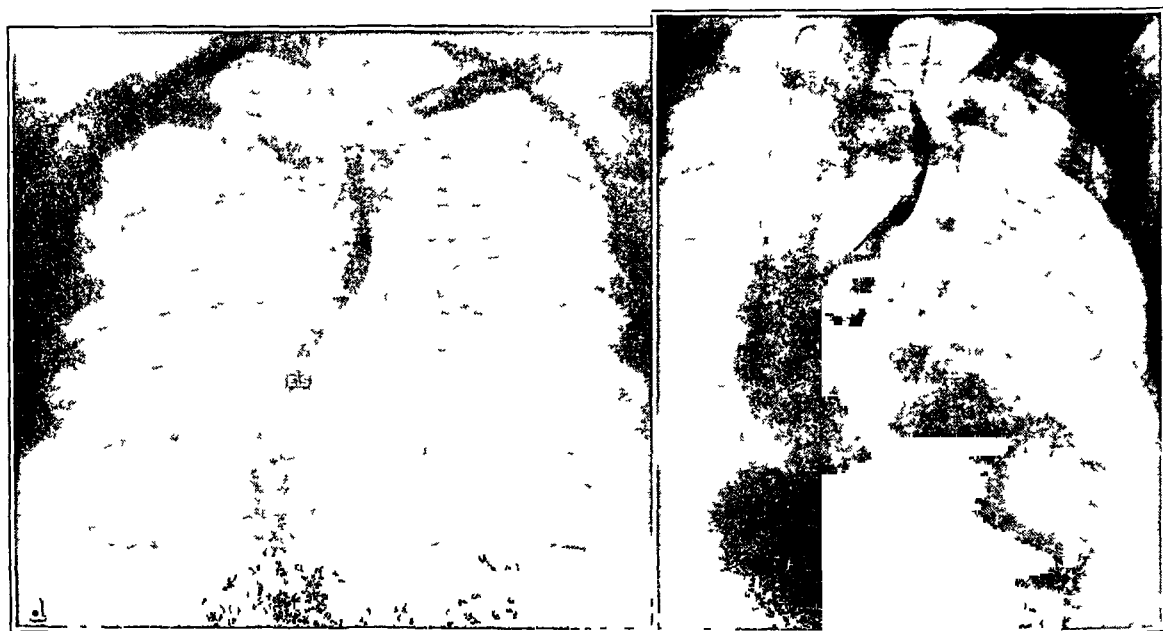


Fig 4—(a) Esophagram, frontal view. The double indenture of the esophagus by the arch and the descending aorta is visible. The lower one half of the esophagus is displaced to the right. In this and in figure 7, *ES* indicates the esophagus.

(b) Esophagram, right anterior oblique view. Note that the esophagus is pushed forward by the arch of the aorta. The descending aorta overlies the spine and appears fusiform.

as well as the origin of the left subclavian artery, could be seen in the left lateral view.

In the right anterior oblique view (fig 3 *a*) the tortuous course of the thoracic aorta was well demonstrated, furthermore, the position of the arch behind the trachea and the absence of an aneurysm of the descending aorta were shown. Finally, in the left anterior oblique view (fig 3 *b*) the aorta exhibited no tortuosity or other unusual features except the straightening and the parallel course of the

two limbs and the clearing of the spine by the descending limb. The diameter of the ascending aorta was within normal limits (3 cm), whereas that of the transverse and the descending portion was larger, measuring 4 cm.

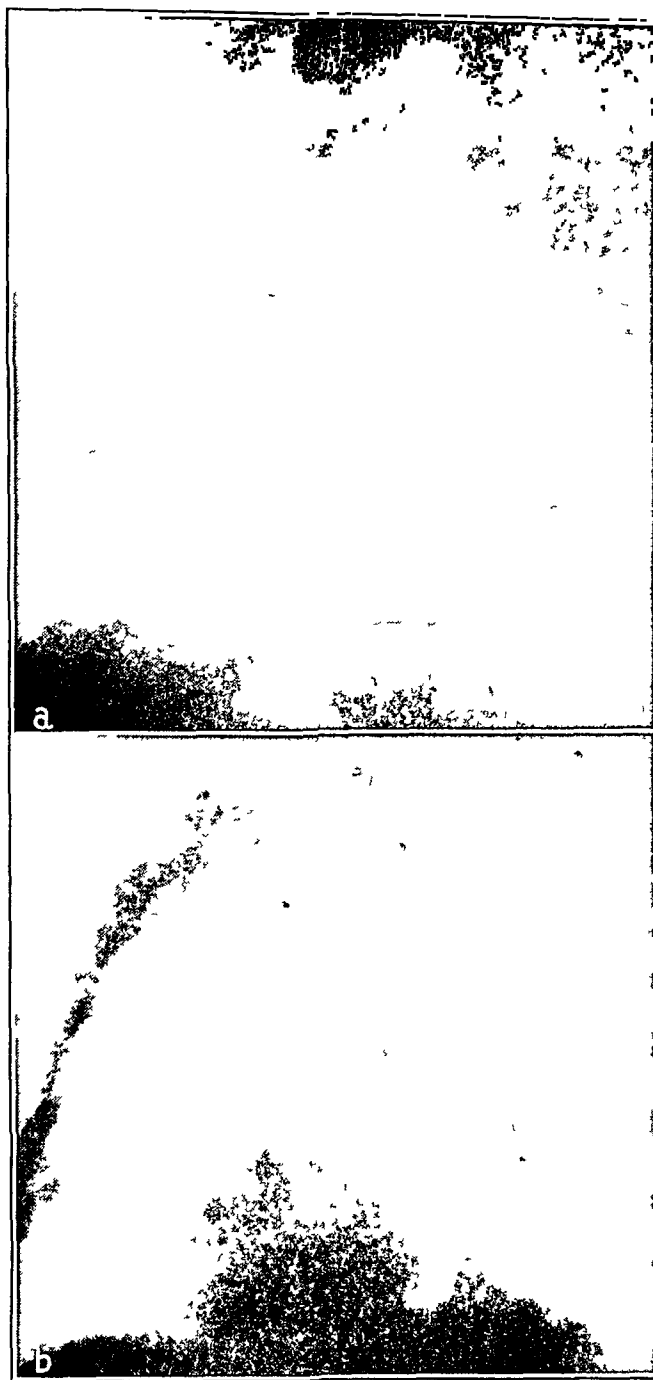


Fig 5—(a) Conventional roentgenogram, left lateral view (target distance 36 inches [91 cm]). The thoracic aorta is poorly defined, and the descending portion, overlying the spine, appears tortuous.

(b) Conventional teleoroentgenogram, left anterior oblique view, at 45 degrees. Note that the ascending and descending limbs of the aorta are close together. The descending aorta does not overlie the spine.

COMMENT

Up to 1932, 100 cases of right-sided aorta had been diagnosed.⁵ In the majority of cases the anomaly was identified at autopsy or in the dissection room, and was rarely recognized clinically. Quain, in his treatise on arteries,⁶ mentioned a case of right-sided aorta seen by Sandifort as early as 1793, during a dissection of the thorax. Since Quain's report, numerous examples have been recorded in the literature, mainly in the journals of anatomy.⁷ However, it was Assman⁸ who, in 1918, first established definite roentgenographic criteria for the diagnosis of this anomaly during life and Arkin⁹ who, in 1926, showed that there were additional roentgenographic findings when a right-sided aorta was associated with persistence, in part or in whole, of the left aortic arch. The number of cases detected during life has increased greatly within the last decade, both because of the establishment of these roentgenographic criteria and because of the routine roentgenographic examination of patients with cardiovascular disease and of those presenting the symptom of dysphagia.¹⁰ In 5,000 roentgen examinations of the chest, Biedermann found 7 cases of right-sided aorta.^{10a} It is to be expected that the extensive use of thoracic roentgenography today, particularly in tuberculosis surveys, will still further increase the frequency with which this congenital anomaly is diagnosed in patients who are asymptomatic.

5 Blackford, L. M., Davenport, T. F., and Bayley, R. H. Right Aortic Arch. Clinical Report of a Case with Associated Anomalies, *Am J Dis Child* **44** 823 (Oct.) 1932.

6 Quain, J. Anatomy of Arteries, in *Elements of Anatomy*, ed 5, London, 1844, vol 1, pt 7.

7 (a) Reid, D. G. Three Examples of a Right Aortic Arch, *J Anat & Physiol* **48** 174, 1914. (b) Blackhall, M. A. Cardiac Malformations with Vascular Anomalies, *J Anat* **62** 227, 1928. (c) Stibbe, E. P. True Congenital Diverticulum of the Trachea in a Subject Showing Also Right Aortic Arch, *ibid* **64** 62, 1929. (d) Priman, J. Notes on Anomalies of Aortic Arch and of Its Large Branches, *Anat Rec* **42** 335, 1929. (e) Sprong, D. H., and Cutler, N. L. A Case of Human Right Aorta, *ibid* **45** 365, 1930.

8 Assman, H. *Klinische Röntgendiagnostik der inneren Erkrankungen*, ed 3, Leipzig, F. C. W. Vogel, 1924, p 103.

9 Arkin, A. Totale Persistenz des rechten Aortenbogens im Röntgenbild, *Wien Arch f inn Med* **12** 385, 1926.

10 (a) Spencer, J., and Dresser, R. Right Sided Aorta, *Am J Roentgenol* **36** 183, 1936. (b) Sprague, H. B., Ernlund, C. H., and Albright, F. Clinical Aspects of Persistent Right Aortic Root, *New England J Med* **209** 679-686, 1933. (c) Friedman, M. Right-Sided Aorta. Report of Two Cases, *Radiology* **25** 106, 1935. (d) Fray, W. W. Right Aortic Arch, *ibid* **26** 27, 1936. (e) Arkin, A. Double Aortic Arch with Total Persistence of the Right and Isthmus Stenosis of the Left Arch, *Am Heart J* **11** 444, 1936. (f) Bedford, D. E., and Parkinson, J. Right-Sided Aortic Arch, *Brit J Radiol* **9** 776, 1936. (g) Garland, L. H. Persistent Right-Sided Aortic Arch, *Am J Roentgenol* **39** 713, 1939.

While the embryonic development of this interesting condition has been adequately treated in the previous reviews,¹¹ the development of a right-sided aorta is more easily understood when it is correlated with other abnormalities of the fourth arch. The embryonic development of anomalies of the aorta is diagrammatically represented in figure 6 *a* to *g*. The fourth right arch is represented by *R*, the right dorsal root by *R'* and the left fourth arch and dorsal root by *L* and *L'*, respectively (fig 6 *a*). If it is postulated that each structure may atrophy in part or in whole, then the following possibilities exist:

1 *R'* may atrophy, leaving *R*, *L* and *L'* intact (fig 6 *b*). The result can be clearly recognized as the normal human aorta, in which the left fourth aortic arch becomes the definitive aorta and the right subclavian artery is formed from the fourth right arch.

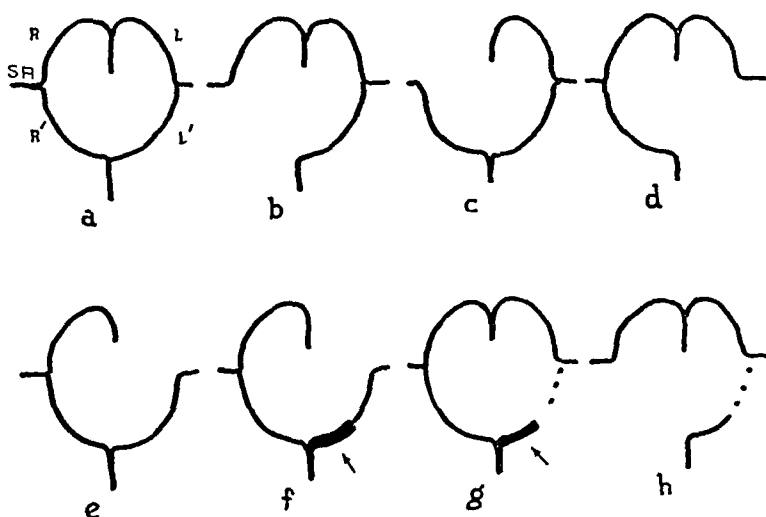


Fig 6—Developmental anomalies of the fourth aortic arch. *a*, double aortic arches, *b*, normal left-sided aorta, *c*, anomalous right subclavian artery, *d*, simple right-sided aorta, *e*, right-sided aorta with an anomalous left subclavian artery, *f*, right-sided aorta with a persisting diverticulum of the left dorsal root (present case), *g*, double aortic arches with an isthmus stenosis of the left arch, and *h*, coarctation of the aorta (adult type). *R* indicates the right aortic arch, *R'*, the right aortic root, *L*, the left aortic arch, *L'*, the left aortic root, and *SA*, the subclavian artery. The arrows point to the diverticulum.

2 *R* may disappear, resulting in the development of an anomalous right subclavian artery (fig 6 *c*).¹² In this abnormality, the right subclavian artery has its origin distal to the left subclavian artery and crosses behind the esophagus to reach the right side.

11 Abbott M. Right Aortic Arch, in Osler, W, and McCrae, T. *Modern Medicine*, ed 3, Philadelphia, Lea & Febiger, 1927, vol 4, p 790. Sprong and Cutler¹⁰ Fray^{10a}.

12 Goldbloom, A. A. The Anomalous Right Subclavian Artery and Its Possible Clinical Significance, *Surg, Gynec & Obst* 34:378, 1922. Carney, J. Anomalous Right Subclavian Artery, *J Anat* 59:265, 1925.

3 L' may drop out, leaving a mirror image of the first type (fig 6 *d*) This is the condition described by Assman⁸ as simple right-sided aorta with symmetric reversal of the brachiocephalic vessels

4 L may regress, leaving R , R' and L' intact (fig 6 *e*) The distal segment, L' , may be incorporated into the right arch, giving a type of right-sided aorta with four separate vessels to the head The last of these is the left subclavian artery, which must cross to the left, posterior to the esophagus This is the mirror image of type 2 (fig 6 *c*) In some instances, however, the distal segment, L' , may dilate and become a diverticulum from which the left subclavian artery takes origin (fig 6 *f*) This is the type first described by Turner in 1863,¹³ and more recently by Arkin,^{10e} as right-sided aorta with a diverticulum of the left descending aortic root The case we have described belongs in this group

5 Finally, if all segments, R , R' , L and L' , persist into adult life there results a double aortic arch (fig 6 *a*)¹⁴ In this type of anomaly the subclavian arteries are separate vessels on each side However, there may be partial atrophy of L' for a short distance distal to the left subclavian artery, and the remaining portion of L' becomes a diverticulum (fig 6 *g*) This is the type described by Arkin^{10e} as a double aortic arch with total persistence of the right arch and stenosis of the isthmus of the left arch This form of left arch has no counterpart on the right, that is, there has never been seen an isthmus stenosis on the right with total persistence of the left arch There is a possibility that its occurrence on the left side is due to simultaneous atrophy of the ductus Botalli Its similarity to coarctation of the aorta of the adult type, in which there is, however, no persisting right arch, can readily be seen (fig 6 *h*)

Interesting speculations have been advanced as to the cause of these congenital anomalies in man It has been postulated by some investigators^{10e} that right-sided aorta results when the left arch is stenosed in part or entirely before the disappearance of the right arch in fetal life, whereas coarctation of the aorta of the adult type (stenosis of the isthmus) is the result when stenosis occurs afterward A second, less plausible, theory¹⁵ relates the persistence of the right aortic arch to a change in the amount of cervical flexure in the embryo, causing pressure on the arches lying in the neck in fetal life This might result in obliteration of the left fourth arch with the right arch left intact

13 Turner, W, cited by Thomson, A Description of the Dissection of a Case of Right Aortic Arch, Glasgow M J **11** 1, 1863

14 Shaw, D L An Aorta with a Double Arch, J A M A **28** 538 (March 20) 1897 Harris, H A, and Whitney, C Heart of a Child Aged Nineteen Months Presenting Right and Left Aortic Arches, Anat Rec **34** 221, 1927 Lockhart, R D Complete Double Aortic Arch, J Anat **64** 189, 1930

15 Congdon, E D Transformation of the Aortic Arch System During the Development of the Human Embryo, Contrib Embryol (nos 65-71) **14** 47, 1922

In summary, there may be three main types of right-sided aorta in adult life

Simple Right-Sided Aorta—In this type the vessel arises normally, but instead of crossing to the left, it arches to the right and backward over the right bronchus and continues downward slightly to the right of the midline. The brachiocephalic vessels are usually symmetrically reversed, consisting of an innominate artery on the left side and a common carotid and a subclavian artery on the right side. The ductus arteriosus, being the surviving left ductus, must cross behind the trachea and esophagus to reach the aortic arch. The diagnosis rests on the following roentgenographic signs: (1) the presence of an abnormal mediastinal shadow near the first right costosternal junction in the frontal view, associated with absence of the usual aortic knob on the left, (2) the close proximity of the two limbs of the aorta in the left anterior oblique view, as normally occurs in the right anterior oblique projection, and the failure of the descending aorta to overlap the spine, and finally (3) as shown in barium studies, the deviation of the esophagus to the left, instead of to the right, with the aortic impression concave to the right as a consequence.

Right-Sided Aorta with Either an Anomaly of the Left Subclavian Artery or a Diverticulum of the Persisting Left Root—The first type is unique only in having the left subclavian artery cross from right to left behind the esophagus. In the second type, emphasized by Arkin, the aorta arches over the right bronchus but is joined behind the esophagus by a diverticulum of the left dorsal root and by the dorsal aorta. Here the left subclavian artery arises from the diverticulum and hence does not cross behind the esophagus. The roentgenographic signs are the same as those for simple right-sided aorta, except that the diverticulum may be seen in the frontal view as a small protuberance in the position normally occupied by the aortic knob and in the right oblique view as a rounded shadow within the retroesophageal portion of the aorta. An additional diagnostic point is that the barium-filled esophagus is deviated anteriorly by the diverticulum, a relationship best seen in the right anterior oblique view (fig 4) ^{10e}

Complete Double Aortic Arch—This type is often associated with other congenital cardiac anomalies which are incompatible with life. However, in some instances it has been reported as an accidental finding in autopsies of patients above 50 years of age, but in these it was unassociated with other cardiac abnormalities. In this type, the aorta ascends to the right and turns backward, dividing into two large trunks which enclose the trachea and esophagus in a vascular ring. These vessels unite beyond the insertion of the ductus Botalli to form the descending aorta. From the right, or posterior, arch, the right sub-

clavian and the right common carotid arteries arise, whereas the left subclavian and the left common carotid arteries are branches from the left, or anterior, arch. The diagnosis is made by finding the shadow of the barium-filled esophagus to be uniformly constricted on all sides at the level of the arch of the aorta. When there is a stenosis of the left arch at the isthmus, the left common carotid artery is the first branch of the aorta and the left subclavian artery, being the surviving left fourth aortic arch, is the second branch. It is connected to the left fourth dorsal root, which becomes a diverticulum, by the fibrous band which is the remains of the isthmus. The roentgenographic signs are the same as those of a simple right-sided aorta with a diverticulum of the left dorsal root.

In our patient, the diagnosis of right-sided aorta was not made from examination of the routine frontal roentgenogram of the chest for two reasons. (1) The small shadow caused by the diverticulum occupied the position of the "aortic knob," simulating it, and (2) the pulsating mass on the lower right cardiac border made the diagnosis of aneurysm seem obvious. This pulsating mass projecting from the mediastinum was shown by visualization studies to be a tortuous and elongated descending aorta. Reports of instances in which the descending aorta curves into the right pulmonary field are rare. In a case reported by Rosler and White¹⁶ in which the roentgenogram was similar to that in our case, the abnormal right mediastinal shadow was ascribed to extreme tortuosity of the descending aorta. In that case, too, aneurysm and right-sided aorta were thought to be excluded because the trachea in the frontal view was not deviated to the left. However since esophageal studies were not reported, the presence of right-sided aorta cannot be ruled out conclusively.

Usually, when the aorta elongates, the descending limb, both on the roentgenogram and at postmortem examination, is seen to describe a large arc toward the left lung. Reflection on the relationship of the aorta to the esophagus and the vertebral column makes it clear why this must necessarily take place in most cases. The esophagus is held by fibrous bands to the right of and slightly anterior to the descending aorta, which lies in the left vertebral gutter. Any tendency of the descending aorta to curve into the right pulmonary field will be interfered with by both the esophagus and the vertebral column, and the vessel will be retained on the left side. However, in the case of right-sided aorta this condition is reversed. The aortic arch crosses obliquely backward and to the right, instead of to the left, and the descending aorta lies mainly

16 Rosler, H, and White, P. Unusual Variations of Roentgen Shadow of Elongated Thoracic Aorta, *Am Heart J* 6 768, 1931

to the right of the esophagus. Thus, when the thoracic aorta elongates it will be pushed into the right pulmonary field, pulling the esophagus with it.

In the present case, contrast cardiovascular roentgenograms satisfactorily demonstrated the size and course of the thoracic aorta and showed that the true aortic knob lay near the right upper border of the cardiovascular silhouette. They showed, furthermore, that the shadow misinterpreted as the left aortic knob was caused by a small diverticulum from the left descending root. This diverticulum could be also seen in the left lateral view, in which it was clearly demonstrated that the left subclavian artery arose from this pouch. The tortuous and elongated descending aorta curved into the right pulmonary field, simulating aneurysm of the aorta. When the routine frontal roentgenogram is reviewed, it is easy to see how the correct diagnosis might have been suggested by the shadow at the first right costosternal junction, the hypoplastic "knob" on the left side and the absence of the descending aorta normally present to the left of the midline. The stridor and dysphagia due to pressure on the trachea and on the esophagus, which may occur in this disorder, giving a clue to its nature, were absent in this case. It is possible, however, that more marked arteriosclerosis of the aorta would produce symptoms by pressure on these organs. Finally, other anomalies of the heart and the intrathoracic blood vessels, which sometimes occur with this disorder, were excluded by cardiovascular visualization.

SUMMARY

A case of right-sided aorta with diverticulum from the left dorsal root is described. By contrast visualization of the cardiovascular system, the size and course of the entire thoracic aorta were graphically demonstrated and the nature of the congenital anomaly was established. The pulsating mass near the right cardiac border which simulated aortic aneurysm was proved to be the tortuous descending aorta. The embryonic development of right-sided aorta and of other congenital abnormalities of the fourth aortic arch is discussed.

LIFE EXPECTANCY IN CONDUCTIVE DISTURBANCES AFFECTING THE VENTRICULAR COMPLEX OF THE ELECTROCARDIOGRAM

I GENERAL CONSIDERATIONS OF BUNDLE BRANCH BLOCK WITH
CONCORDANT AND WITH DISCORDANT GRAPHS AND THE
WIDE S WAVE PATTERN, BASED ON 1,611 CASES

FREDRICK A WILLIUS, MD

THOMAS J DRY, MB

AND

RICHARD REESER JR, MD

Fellow in Medicine, the Mayo Foundation
ROCHESTER, MINN

The reader who surveys critically the present day voluminous literature dealing with bundle branch block and allied disturbances does so with an overpowering sense of confusion and with the realization that that the subject is one demanding clarification and simplification. The majority of published investigations deal either with the experimental production of bundle branch defects in animals or with the study of clinical electrocardiograms shuffled into various classifications by various authors.

Without doubt the outstanding contribution in the field of disturbances of conduction is the careful and painstaking histopathologic investigations of Yater and his co-workers¹. In fact, with the exception of certain experimental studies on animals, which obviously are not strictly comparable, their work is the only existent groundwork for the comparison and classification of clinical electrocardiograms. Mahaim's²

From the Section on Cardiology (Drs Willius and Dry), the Mayo Clinic

1 (a) Yater, W M, Cornell, V H, and Claytor, T Auriculoventricular Heart Block Due to Bilateral Bundle Branch Lesions. Review of the Literature and Report of Three Cases with Detailed Histopathologic Studies, *Arch Int Med* **57** 132 (Jan) 1936 (b) Yater, W M Pathogenesis of Bundle Branch Block. Review of the Literature, Report of Sixteen Cases with Necropsy and of Six Cases with Detailed Histologic Study of the Conduction Systems, *ibid* **62** 1 (July) 1938

2 Mahaim, I Les maladies organiques du faisceau de His-Tawara Les syndromes coronaire L'endocardite septale L'infarctus septal (étude clinique et anatomique), Paris, Masson & Cie, 1931, Nouvelles recherches sur les lésions du faisceau de His-Tawara (deuxième mémoire), le bloc de branche gauche et sa pathogène, la septite mitrale, *Ann de méd* **38** 185, 1935

work is also outstanding in this field. Owing to the fact that studies of the conducting system of the heart by means of serial sections consume vast amounts of time and demand extraordinary patience, reliable investigations have been few.

Yater and his co-workers¹ reported 9 cases in which the conduction system was completely studied by serial sections, in 3 cases auriculo-ventricular heart block was present and in 6 cases bundle branch block. In all of the first 3 cases published (those of auriculoventricular heart block) Yater and his co-workers^{1a} concluded that the pathogenic factor was probably disease of the coronary arteries and that the condition is due in most instances to lesions, partial or complete, in both bundle branches, although they expressed the belief that destructive lesions of the terminal portion of the bundle of His may also produce such varying ventricular complexes.

Of the 6 cases of bundle branch block studied by serial section, Yater concluded that both branches were affected in each case, but it was always possible to state which of the two branches was more seriously damaged. The lesion consisted of fibrosis in all cases. In most of the cases it seemed proper to attribute the pathologic condition of the bundle branch and myocardial disease to disease of the coronary arteries. In commenting on the frequency of greater damage to the right bundle branch than to the left in cases of rheumatic heart disease, Yater concluded that perhaps the arteritis of rheumatic causation, involving more prominently the intramyocardial arteries than the large subepicardial vessels, more often affects the entire thickness of the interventricular septum and would be more likely to destroy completely the right bundle branch in its intramyocardial portion than it would the subendocardial portion, that is, the main portion of the extensive left branch. In cases of coronary disease or hypertension or both, the brunt of the strain, either vascular or hypertensive, is borne by the left ventricle, therefore, it is fair to assume that the nutrition of the left bundle branch would be much more likely to suffer severely than that of the right branch. From a study of these 6 cases, Yater expressed the belief that the amplitude of the ventricular complex is not entirely dependent on the state of the bundle branches in the human subject.

It is our intention, in so far as possible, to classify our clinical electrocardiograms according to the system used in the cases published by Yater, in which lesions were demonstrated involving the bundle branches bilaterally and in which one branch was more extensively involved than the other. The electrocardiograms in his first 3 cases were all representative of right bundle branch block. The QRS intervals ranged from 0.12 to 0.16 second, and the amplitude of the complexes varied considerably. However, in all cases the T waves were directed opposite to the QRS

complexes in leads I and III. In these cases the right bundle branch was predominantly involved.

The last 3 cases were all examples of left bundle branch block. The QRS intervals were recorded as 0.13, 0.12 and 0.16 second, respectively, a variation of the amplitude of the QRS complexes occurred, and notching of their components was present in only 1 case. The T waves bore a direction opposite to the QRS complexes in leads I and III. Preponderant damage was demonstrated in the left bundle in the first 2 cases, whereas in the last case only moderate involvement of both branches was found.

In our discussion of bundle branch block we unequivocally accept the new terminology of the condition.³ Many terms have been used denoting presumed variations in disturbances of cardiac conduction, based largely on electrocardiographic configuration. They comprise "arborization block", "bundle branch block," typical, atypical and indeterminate, heterogeneous and homogeneous, complete and incomplete, "intraventricular block," and other terms.

Since Carter's⁴ designation, in 1918, of definite graphic criteria for the recognition of bundle branch block, the cardiologist has been conscious of a definite electrocardiographic pattern that is glaringly impressive and is a remarkable departure from the normal electrocardiogram and those with lesser graphic variations. Recognition of this distinct form has resulted in the unwillingness of many cardiologists to consider more attenuated forms of this pattern as exemplifying the same condition. Carter's criteria included a widening of the QRS complex beyond 0.1 second and notching, preponderance of the ventricle supplied by the uninterrupted bundle branch, either right or left axis deviation with the dextrocardiogram appearing in cases of left bundle branch block and with the levocardiogram in cases of right bundle branch block (now reversed by present day concepts), exaggeration of the amplitude of

3 Fahr, G. An Analysis of the Spread of the Excitation Wave in the Human Ventricle, *Arch Int Med* **25** 146 (Feb) 1920. Oppenheimer, B. S., and Pardee, H. E. B. The Site of the Cardiac Lesion in Two Instances of Intraventricular Heart Block, *Proc Soc Exper Biol & Med* **17** 177, 1920. Barker, P. S., Macleod, A. G., and Alexander, J. The Excitatory Process Observed in the Exposed Human Heart, *Am Heart J* **5** 720, 1930. Wilson, F. N., Macleod, A. G., and Barker, P. S. The Order of Ventricular Excitation in Human Bundle Branch Block, *ibid* **7** 305, 1932. Marvin, H. M., and Oughtersen, A. W. The Form of Premature Beats Resulting from Direct Stimulation of the Human Ventricles, *ibid* **7** 471, 1932. Vander Veer, J. B. Premature Beats Produced by the Mechanical Stimulation of the Exposed Human Heart, *ibid* **8** 807, 1933.

4 Carter, E. P. Further Observations on the Aberrant Electrocardiogram Associated with Sclerosis of the Atrioventricular Bundle Branches and Their Terminal Arborizations. Clinical and Histologic Report of a Case in Which Such Aberrant Complexes Were Obtained, *Arch Int Med* **22** 331 (Sept) 1918.

all ventricular deflections, including the T wave, and the T wave directed opposite to the main portion of the QRS deflection

Certain modifications of these criteria are now generally accepted, namely, the requirement of complexes of high amplitude is no longer demanded. It is also questionable whether marked notching of the QRS complex is requisite provided that the QRS interval is prolonged to 0.12 second or more.

In 1920 Wilson and Herrmann,⁵ in a significant publication, concluded that complete bundle branch block produces characteristic changes in the form of the ventricular complex, both in animals and in man, and accepted Carter's criteria for man as correct. They further concluded that delayed conduction of the impulse through the branches of

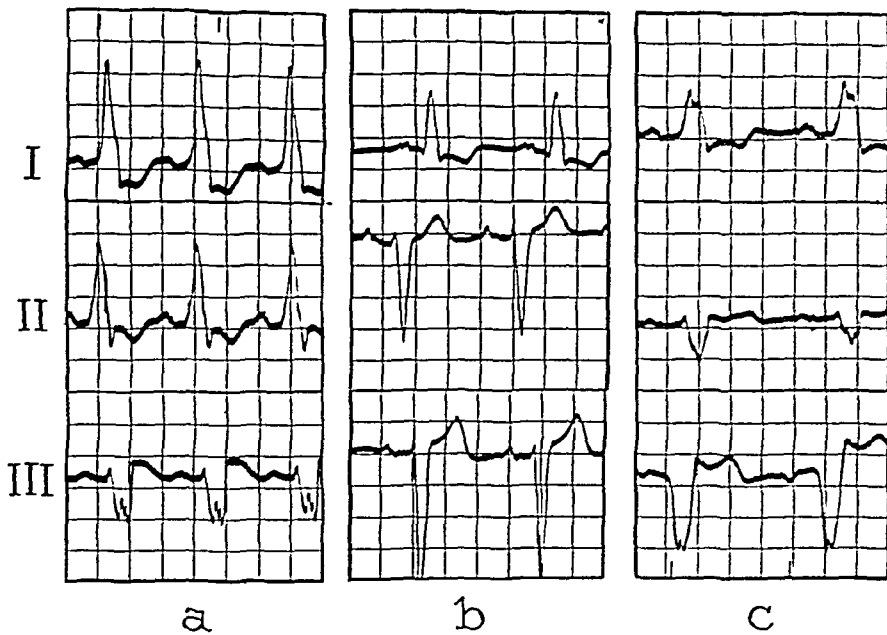


Fig 1—Varieties of left bundle branch block with concordant graphs, showing differences in the amplitude of the QRS deflections and in the width of the QRS complexes. In each case the T waves in leads I and III are opposite in direction to the main deflection of the QRS complex, and in each case left axis deviation exists.

the auriculoventricular bundle (incomplete bundle branch block) produces ventricular complexes which are transitional in form between the normal ventricular complex and complexes characteristic of complete bundle branch block.

We believe, in view of the studies of Yater and of Mahaim, that certain modifications of the foregoing concept are desirable. We question particularly the modification of the term "bundle branch block" by the terms "complete" and "incomplete," feeling doubtful whether the

5 Wilson, F. N., and Herrmann, G. R. Bundle Branch Block and Arborization Block, *Arch Int Med* 26:153 (Aug) 1920.

electrocardiogram is uniformly able to differentiate accurately between complete bundle branch interruption and partial interruption or varying degrees of the latter. This objection is based on the universal bilaterality of lesions of the conduction system and the frequent complete obliteration of one branch, which result in electrocardiograms departing only in accentuation of form from those generally recognized as representative of the classic type of bundle branch block.

It is our contention, therefore, that "bundle branch block" should be represented not only by the classic electrocardiograms universally acknowledged to meet these requirements but also by some of those which have been classed as representing intraventricular block, namely,

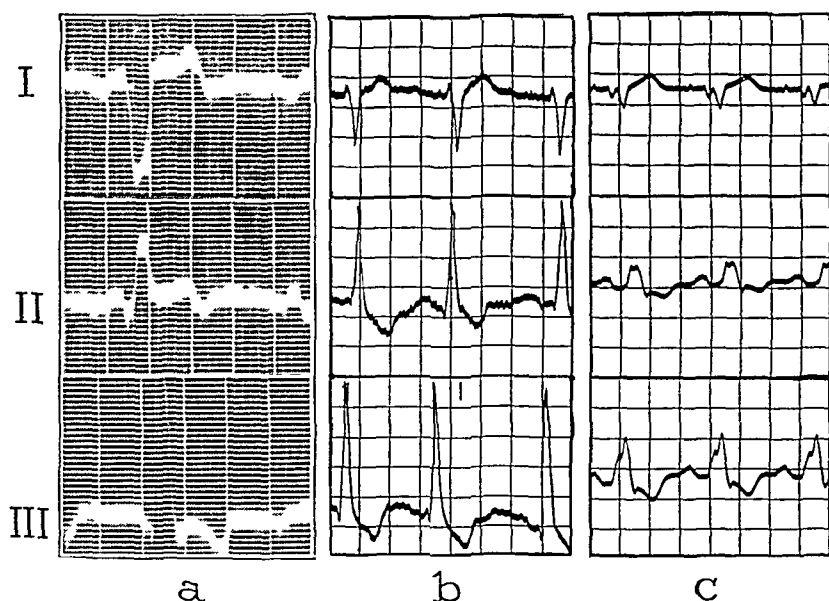


Fig 2—Varieties of right bundle branch block with concordant graphs showing differences in the amplitude of the QRS deflections and in the width of the QRS complexes. In each case the T waves in leads I and III are opposite in direction to the main deflections of the QRS complex, and in each case right axis deviation exists.

those of lesser amplitude and with shorter QRS intervals (beyond 0.10 second), with the T wave (figs 1 and 2) directed opposite to the main deflection of the QRS complex in leads I and III (as in the classic type of bundle branch block), they may show left or right axis deviation according to the branch predominantly affected, without, however, necessarily displacing the typical levocardiogram or dextrocardiogram, notching or slurring may or may not be present. Electrocardiograms exhibiting a spread of the QRS complex beyond 0.10 second, regardless of the amplitude of the ventricular complex, but not associated with directional changes of the T wave opposite to the main deflection of the

QRS complex in leads I and III (fig 3) and not necessarily associated with definitive axis deviation must still be regarded as characteristic of bundle branch block, but it is our contention that they should be distinguished from electrocardiograms occurring in cases of the classic variety of conduction disturbance as already defined. This separation indeed, is not artificial, for not only are the electrocardiographic patterns different in their basic configuration but the life expectancy curves of patients who have them are distinctly divergent in their trends.

In keeping, then, with our original aim of simplifying the nomenclature and of avoiding as far as possible the introduction of new termi-

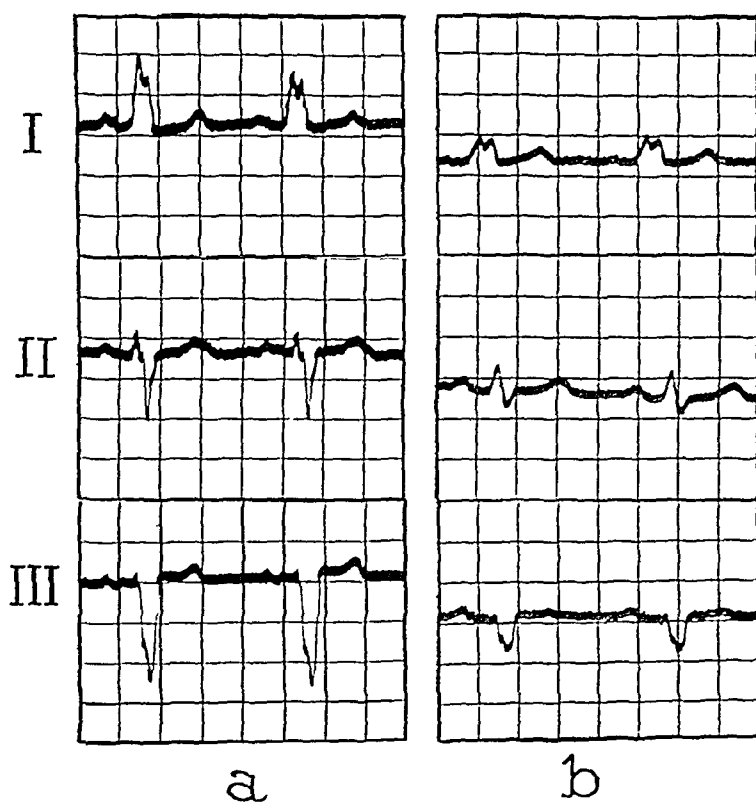


Fig 3—Varieties of bundle branch block with discordant graphs showing differences in the amplitude and in the width of the QRS complexes. The T waves in lead I are in the same direction as the major deflection of the QRS complex. Left axis deviation exists in the tracings, but this is not an essential requirement for the diagnosis of bundle branch block with discordant graphs.

nology, it occurred to us that the terms "concordant" and "discordant" originally employed by Lewis,⁶ in 1916, to distinguish between the more typical and the less classic forms of electrocardiograms obtained on experimental animals, could be applied adequately to differentiate these two varieties of bundle branch block, the term "concordant" being appended to the classic variety of bundle branch block. The term "intra-

6 Lewis, T. The Spread of the Excitatory Process in the Vertebrate Heart. Phil Tr Roy Soc, London 207 221, 1916.

ventricular block" is undesirable because all disturbances of conduction affecting the QRS complex are indeed examples of intraventricular block

Now in the consideration of any representative series of cases in which there are exhibited conductive disturbances affecting the ventricular complex, it will soon become apparent that the two types just defined (bundle branch block with concordant graphs and bundle branch block with discordant graphs) will not account for all cases in which the QRS interval is prolonged beyond 0.10 second. Thus there is the now

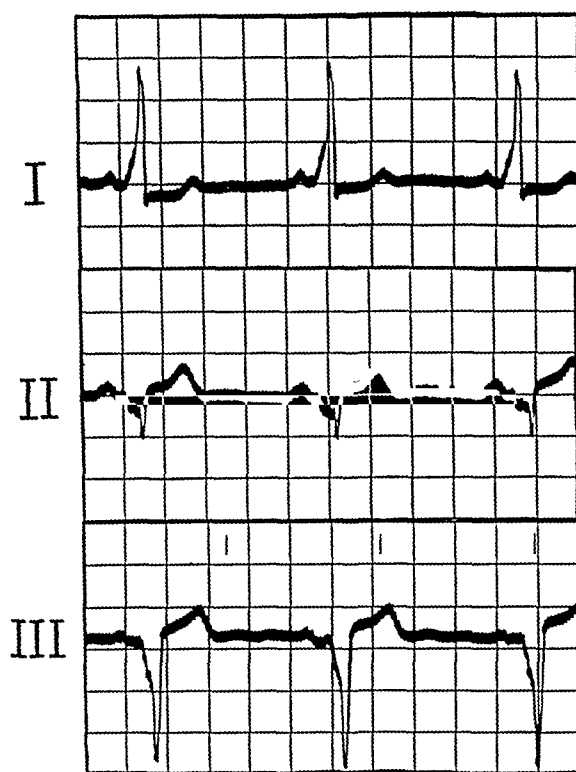


Fig. 4—This rare type of abnormality is associated with a widening of the QRS complex and an unusually short PR interval

well recognized, though rare, electrocardiographic pattern described by Wilson,⁷ in 1915, in which the ventricular complex resembles that seen in cases of bundle branch block but is associated with a short PR interval (fig. 4)

The remainder of tracings not falling in the aforementioned three categories also possess characteristics which warrant their classification, at least for the time being, in a separate group. We refer specifically

⁷ Wilson, F. N. A Case in Which the Vagus Influenced the Form of the Ventricular Complex of the Electrocardiogram, *Arch. Int. Med.* **16**: 1008 (Dec.) 1915

to the electrocardiographic pattern in which the abnormal width of the QRS complex is solely dependent on the S wave, the R component of the ventricular complex being essentially normal. It has been referred to as the pattern for the "rare type" of bundle branch block (which certainly it is not). The picture is so characteristic that it is recognizable at a glance. It is best seen in lead I, and usually also in lead II. It is in a sense the mirror image of the type of prolonged QRS pattern associated with the short PR interval, for whereas the R wave is widened at the expense of the PR interval in the latter, the S wave is widened

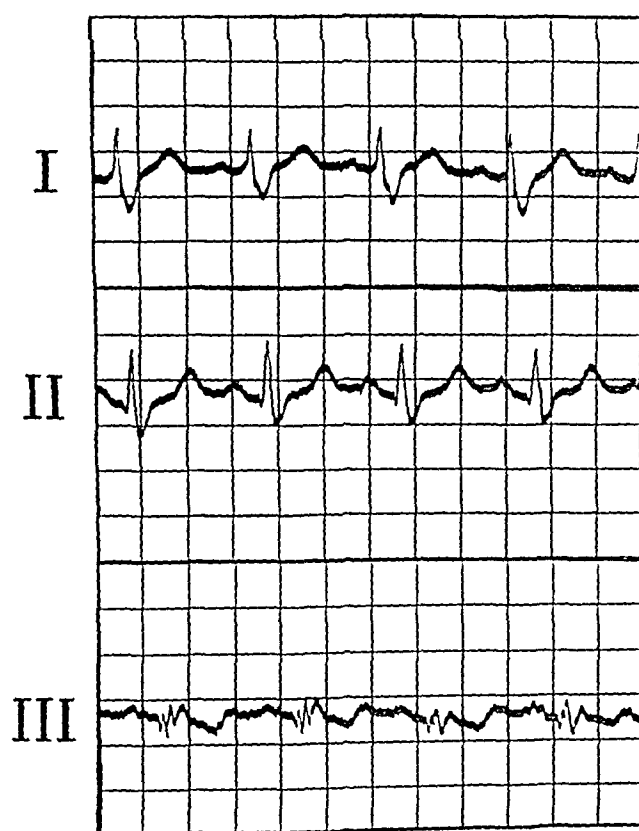


Fig 5—Ventricular conduction disturbance with wide S wave pattern. The configuration of this pattern is remarkably uniformly maintained in leads I and II, while lead III shows considerable variation.

at the expense of the RT interval in the former. The differences in the electrocardiograms under discussion are clearly shown in figure 5.

Throughout the literature dealing with bundle branch conduction patterns the last-named group has, in all but a few instances, been indiscriminately considered along with the patterns for the better known conduction defects affecting the ventricular complex and has been regarded by most writers, moreover, as having the same clinical significance as the pattern for bundle branch block in its conventional form.

One of the primary considerations motivating our present survey is an attempt to determine the fate of persons who possess this electro-

cardiographic pattern and to compare it, on the one hand, with that of persons whose electrocardiograms conform to the pattern for the more conventional type of bundle branch lesions and, on the other, with predictions of so-called normal life expectancy as a control

As far back as 1925, Oppenheimer, Rothschild and Mann⁸ commented on this type of electrocardiogram and intimated a relative benignity in the clinical course of patients exhibiting it, subsequently, Von Deesten and Dolganos,⁹ as well as Wood, Jeffers and Wolferth,¹⁰ also indicated in follow-up studies that an electrocardiographic pattern of this type often occurred in the absence of other evidence of organic heart disease, lending support, therefore, to a viewpoint diametrically opposed to that which has been current regarding disturbances of conduction affecting the ventricular complex in general

The urgency for further information relative to the clinical significance of the electrocardiographic pattern is, therefore, apparent. Certain theoretic considerations relative to the interesting phenomenon will be discussed in a subsequent publication, but for the present we shall accept it as indicating a form of disturbance of conduction and confine ourselves to the practical significance of this type of electrocardiogram as it is encountered in the practice of clinical cardiology

It is surprising that no special nomenclature has been employed in the description of this pattern. In so far as it is characteristic at least in its electrocardiographic configuration (and admitting the undesirability of introducing new descriptive terms when so many are already in use) we feel that it does deserve discrimination in its description. We propose to designate this electrocardiographic pattern simply as 'the wide S wave pattern,' which is all that it is in reality (recognizing it as a suggestive indication of a disturbance of conduction affecting the ventricular complex of the electrocardiogram), much in the same sense as one speaks of a "lengthened Q₃ pattern" (recognizing this as a suggestive relic of a myocardial infarct involving the posterior basal portion of the left ventricle)

MATERIAL AND METHODS OF EVALUATING DATA

A follow-up study was conducted on all patients examined at the Mayo Clinic between Jan 1, 1915 and Dec 31, 1934, inclusive, and on some patients examined in 1935 presenting the various forms of conduction disturbances as defined by us

8 Oppenheimer, B. S., Rothschild, M. A., and Mann, H. Cardiographic Differentiation of a Sub-Group of Intra-Ventricular Block with Observations on the Prognosis, *J. Clin. Investigation* **1** 592, 1925

9 Von Deesten, H. T., and Dolganos, M. Atypical Bundle Branch Block with a Favorable Prognosis, *Am. J. M. Sc.* **188** 231, 1934

10 Wood, F. C., Jeffers, W. A., and Wolferth, C. C. Follow-Up Study of Sixty-Four Patients with a Right Bundle Branch Conduction Defect, *Am. Heart J.* **10** 1056, 1935

under the terms bundle branch block with concordant graphs, bundle branch block with discordant graphs and the wide S wave pattern. Those whose records did not contain the necessary follow-up data were traced by letter, and accordingly it was possible to determine the condition of health of 1,611 patients. In a certain number of instances, however, while the information indicated that the patient concerned had died, the date of his demise was not definitely stated, and such cases were discarded in the study referring to life expectancy, leaving 1,476 cases for the computation of data on life expectancy.

According to the criteria for classification already defined, these 1,611 cases were distributed as follows: bundle branch block with concordant graphs, 756 cases (of which 23 were examples of right bundle branch block and 733 of left bundle branch block), bundle branch block with discordant graphs, 363 cases, and the wide S wave pattern, 492 cases.

In the analysis of our material we have deviated somewhat from the method employed in most follow-up studies, as reported in the literature. In many such studies, for example, it has been customary to consider only the patients who have died, to determine the average duration of life of those patients and to base conclusions regarding the mortality of the condition studied on these determinations. There is an actuarial objection to this procedure, based on the fact that this average figure obviously does not represent the average duration of life for the particular lesion under consideration in so far as some patients belonging to the group studied still are living and the duration of life of the person still alive is entirely unknown. Yet the reader is at least tempted to conclude (and usually does) that the average duration, so stated, will apply to any group of patients with a similar lesion. If, on the other hand, the investigator were to continue his follow-up study on a group of patients (sufficiently large to allow for statistical accuracy) until they had all died, then only would the average duration of life for that lesion be represented by such a figure. This, of course, is hardly possible. There is an objection also on the ground that the average duration of life, even were it accurately determined, would not necessarily supply the information which would be of assistance in determining the prognosis for the individual patient.

As the analysis of our data is intimately concerned with the question of life expectancy and prognosis, we resorted through the assistance of the department of biometry and medical statistics of the Mayo Clinic to the method employed in actuarial practice. This method is governed by mathematical laws which allowed computations of the desired data even though a considerable number of the patients falling within the scope of our study were still living at the time the investigation was conducted.

ETIOLOGIC FACTORS

Sex Distribution—In keeping with the incidence of coronary disease (which is the most common etiologic factor concerned in disturbances of conduction of all kinds), table 1 shows a marked preponderance of males over females in all groups studied. This is particularly noticeable in the group with the wide S wave pattern, a fact which may be of importance in the consideration of the genesis of the lesion associated with this pattern.

Age Distribution—Table 1 also indicates the distribution by age in the three groups. It will be seen that all types of conduction disturbances affecting the ventricular complex are more common after middle

life (especially between the ages of 50 and 70) In fact, the average age at the time of the diagnosis of the lesion is strikingly similar in the three groups 58.6 in the case of bundle branch block with concordant graphs, 58.3 in the case of bundle branch block with discordant graphs and 59.3 in the case of the wide S wave pattern

Associated Clinicopathologic Findings—Our study confirmed the observation of others that by far the majority of bundle branch lesions result from changes incidental to coronary disease, independently or in association with hypertension When rheumatic heart disease plays any part in its production, bundle branch block with concordant graphs often assumes the form of right bundle branch block This is in keeping with the histopathologic studies of Yater Of the entire series of 1,611

TABLE 1—*Age and Sex Distribution*

Age at Diagnosis, Years	Concordant Bundle Branch Block		Discordant Bundle Branch Block		Wide S Wave Pattern	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
0-9	5	0.7	2	0.6	2	0.4
10-19	11	1.5	8	2.2	2	0.4
20-29	29	3.8	13	3.6	7	1.4
30-39	87	11.5	55	15.2	19	3.9
40-49	245	32.4	103	28.4	56	11.4
50-59	274	36.2	124	34.2	139	28.3
60-69	93	12.3	50	13.8	182	37.0
70-79	12	1.6	8	2.2	76	15.4
80-89					9	1.8
Total	756	100	363	100	492	100
Youngest	10	years	15	years	9	years
Oldest	88	years	84	years	88	years
Average age	58.6	years	58.3	years	59.3	years
Males	508	67	259	71	395	80
Females	248	33	104	29	97	20
Total	756	100	363	100	492	100

patients, coronary and hypertensive heart disease was considered the etiologic factor in 259 (34 per cent) of the 756 patients with bundle branch block with concordant graphs, in 90 (25 per cent) of the 363 patients with bundle branch block with discordant graphs and in 92 (19 per cent) of the 492 patients with the wide S wave pattern Coronary sclerosis was regarded as the cause in 296 (39 per cent), 142 (39 per cent) and 141 (29 per cent), respectively, and hypertension alone was considered the etiologic factor in 98 (13 per cent), 41 (11 per cent) and 53 (11 per cent), respectively Otherwise stated, coronary disease and hypertension, either separately or in association with one another, were stated as the etiologic factor in 86 per cent of patients with bundle branch block with concordant graphs, in 75 per cent of patients with bundle branch block with discordant graphs and in 58 per cent of patients with the wide S wave pattern

Rheumatic heart disease was present in 85 patients (11 per cent) with bundle branch block with concordant graphs, in 33 (9 per cent) with bundle branch block with discordant graphs and in 44 (9 per cent) with the wide S wave pattern. In the last-named group mitral disease predominated (25 of the 44 patients, while 3 additional ones had mitral stenosis in association with aortic disease), whereas in the other two groups taken together aortic disease predominated over mitral disease in the proportion of 64 to 32 patients. There were 22 patients (3 per cent) with syphilitic aortitis in the group with bundle branch block with concordant graphs, 7 (2 per cent) in the group with bundle branch block with discordant graphs and 6 (1 per cent) in the group with the wide S wave pattern. The remainder comprised persons with congenital heart disease and various miscellaneous etiologic factors.

SURVIVAL CURVES

In figure 6 are shown the survival curves calculated for the three groups showing types of disturbance of conduction and for the normal population of similar sex and age¹¹. Each curve gives the expected number of persons out of 100 who will be living for each consecutive year after the diagnosis is made. It is seen that the survival curve for each of the groups of patients is considerably below that for the normal population and that the lowest level of survivors is found in the group with bundle branch block with concordant graphs, the next lowest in that with bundle branch block with discordant graphs and the highest in that with the wide S wave pattern. The steepest descent in the survival curve, indicating a high death rate, is seen in the first year. This applies to all of the three groups of defects of conduction studied. After the first year the curves tend to level off. One year after the diagnosis has been made, 80 per cent of patients with the wide S wave pattern, 67 per cent of those with bundle branch block with discordant graphs and 57 per cent of those with bundle branch block with concordant graphs are living. After the first year, the group with the wide S wave pattern maintains practically a constant death rate from year to year which is but slightly greater than that for the normal population. After ten years 38 per cent of the patients in this group are still alive, as compared with 65 per cent in a normal population of the same age, the discrepancy in the number of those surviving among the group with the wide S wave

¹¹ The methods of calculating the mortality and survival rates followed the regular principles used in actuarial practice (for example, "Construction of Mortality Tables from the Records of Insured Lives," New York, The Actuarial Society of America, 1922), and the calculations for this study were made in the division of biometry and medical statistics of the Mayo Clinic.

pattern as compared with those among the normal population being accounted for mainly by the high mortality rates in the first year after the discovery of the defect of conduction

In the groups with bundle branch block of the concordant and of the discordant type, the annual death rate is greater than that for the group with the wide S wave pattern not only during the first year but also in succeeding years, so that only 16 and 26 per cent of the respective original groups were alive ten years after the diagnosis had been established, figures which reflect a more serious prognosis for these groups than for the group with the wide S wave pattern. One difference to be noted between the two groups is that whereas the survival curve for the group with bundle branch block with discordant graphs after

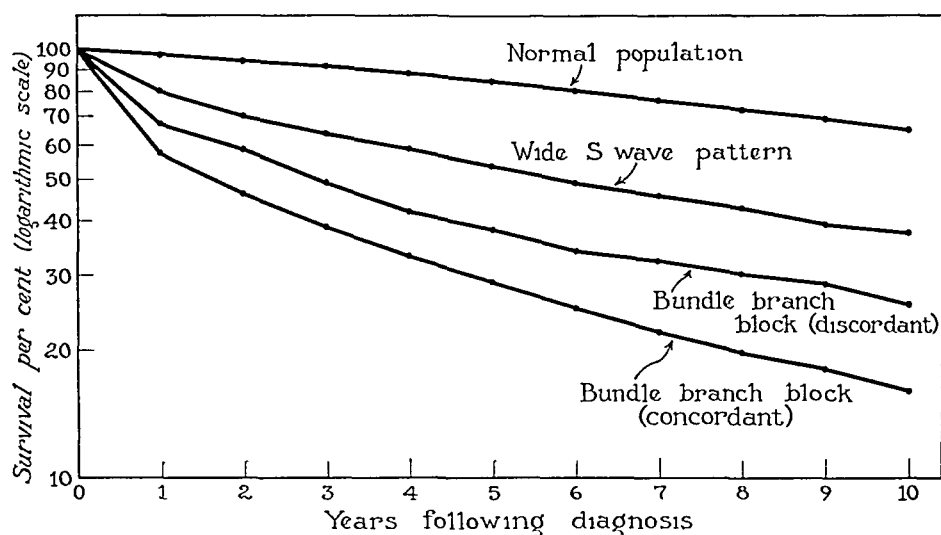


Fig 6—Survival curves of groups of patients with bundle branch block with concordant graphs, bundle branch block with discordant graphs and the wide S wave pattern as compared with that of a normal population of the same age and sex

about the fifth year approximates normal, that for the group with bundle branch block with concordant graphs continues to show a higher mortality, as indicated by the greater steepness of the corresponding curve

MORTALITY

In tables 2 and 3 the mortality experience is presented in the form of annual death rates for various years after the diagnosis was made. In table 2 it is seen that in the first year the mortality rate for bundle branch block with concordant graphs is 43 per cent, for bundle branch block with discordant graphs 33 per cent and for the wide S wave pattern 20 per cent. These are to be contrasted with a death rate of

about 3 per cent for a normal white male population of similar age. The annual death rate for the persons who survive one year is seen to be 20 per cent for those with bundle branch block with concordant graphs, 13 per cent for those with bundle branch block with discordant graphs and 12 per cent for those with the wide S wave pattern. The death rates themselves are not so great after the first year following diagnosis as they are for the first year, but the death rates for the three types have about the same ratio to one another as for the first year after diagnosis. After the fourth year it is seen that the annual rates for the

TABLE 2—*Annual Death Rate from All Causes, Per Cent, Comparison of Patients with Conductive Defects and Normal Population*

Years After Diagnosis	Annual Death Rate, Per Cent			
	Concordant Bundle Branch Block	Discordant Bundle Branch Block	Wide S Wave Pattern	Normal Population
0-1	42.5	32.5	19.9	2.6
1-2	19.9	13.0	12.2	2.8
2-5	14.7	13.9	8.6	3.3
5-10	11.3	7.5	7.3	4.6

TABLE 3—*Annual Death Rate from Cardiac Causes, Per Cent, Comparison of Patients with Conductive Defects and Normal Population*

Years After Diagnosis	Annual Death Rate, Per Cent Conductive Defects *			
	Concordant Bundle Branch Block	Discordant Bundle Branch Block	Wide S Wave Pattern	Normal Population
0-1	41.0	30.7	17.8	0.9
1-2	17.6	10.5	9.7	1.0
2-5	11.8	11.0	5.5	1.1
5-10	7.0	3.0	2.8	1.2

* The death rate from cardiac causes in the groups of patients was obtained by correcting the rate from all causes as observed (table 2) by rates for causes other than cardiac in the general population.

groups with the wide S wave pattern and bundle branch block with discordant graphs are both about 7 per cent, whereas the group with bundle branch block with concordant graphs has an annual death rate of about 11 per cent, as contrasted with a rate of about 5 per cent for the normal population.

In table 3 is made the same sort of comparison as in table 2, except that the rates are confined to deaths from cardiac causes. The contrast between the mortality rates of patients with disturbances of conduction and those of the normal population is naturally much greater when the death rates from cardiac causes alone rather than rates from all causes are considered, but the general comparisons are similar to what was shown in table 2.

CONDITION OF THE PATIENT IN THE SERIES
AT THE LAST REPORT

Table 4 summarizes the facts relative to the condition of all patients at the time of the last report. The prognostic trend inherent in this table coincides with the facts revealed by the life expectancy curves already discussed. The column referring to the deaths due to unknown causes requires some comment. Instances in which the death was presumably primarily from a cardiac cause but in which this fact is not so stated in the follow-up information are included in this group. The clinical findings at the time of the last examination would tend to indicate that the percentage of deaths due to cardiac causes in this group is fairly high. In so far as this is applicable to all three types of conductive disturbance studied, the true facts remain undistorted from the general standpoint of life expectancy and prognosis.

TABLE 4—*Condition at Last Report*

	Concordant Bundle Branch Block		Discordant Bundle Branch Block		Wide S Wave Pattern	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Living, well	47	6.2	46	12.7	125	25.4
Living, well with rest	48	6.3	31	8.5	46	9.3
Living, not well	14	1.9	9	2.5	11	2.2
Living, condition unknown	2	0.3	2	0.6	2	0.4
Dead, cause cardiac	334	44.2	122	33.6	95	19.3
Dead, cause other than cardiac	57	7.5	48	13.2	85	17.3
Dead, cause unknown	254	33.6	105	28.9	128	26.0
Total	756	100.0	363	100.0	492	100.0

COMMENT

The discovery of a conductive defect of any type is to be regarded, until proved otherwise, as indicative of a lesion which has inflicted damage not only on the bundle of His or its ramifications but also on the myocardium itself. The high incidence of clinically demonstrable organic heart disease among persons exhibiting one or another electrocardiographic pattern indicative of a conductive defect soon fostered the belief that such defects were invariably of serious prognostic significance. Indeed, when one considers that all pathologic lesions capable of inflicting myocardial damage (be it the result of arteriosclerosis, of an inflammatory process such as rheumatic disease or syphilis or of hypertension) are inherently progressive in nature, there seems to be good justification for such a belief.

The one factor that was not appreciated for a long time was the extent to which the cardiovascular apparatus is capable of readjusting itself to processes, even though their natural tendency may be toward progression. The eventual means of readjustment lies in the process of revascularization of regions deprived of their original blood supply.

In this connection it is to be recalled that the conductive tissues are more highly specialized than the rest of the myocardium, so that restoration of function after injury is less likely to occur in the former than in the latter. One needs only to be reminded of the evolution of the present day attitude toward the clinical event of acute coronary occlusion. Not much more than two decades ago it was universally believed that the prolongation of life was incompatible with such an occurrence. Now it is known that this is far from the truth. And indeed are not conductive disturbances in the vast majority of cases simply another manifestation of the same process which so frequently culminates in acute myocardial infarction, namely, coronary sclerosis? Yates went so far as to suggest that the damage to the conductive system, as encountered in rheumatic heart disease, is the result of a similar interference with its blood supply.

In short, it has become clear that the prognosis of heart disease is determined by the progress of the underlying pathologic process (against such readjustments as the coronary system can make) rather than by the mere evidence demonstrable by instrumental means that a pathologic process actually exists. Moreover, in the evaluation of instrumental evidence of heart disease, due allowance must be made for the sampling among persons who are submitted for electrocardiographic study. The files of any electrocardiographic laboratory are liable to be replete with tracings of patients in whom cardiac disease is either manifest or suspected.

In keeping with this revised viewpoint relative to the life history of coronary disease and with the wider application of the electrocardiogram in diagnosis, it has become apparent that among patients with conductive disturbances, regardless of the type, there are instances (as there are instances of patients who have had a coronary occlusion) in which the clinical course proves relatively favorable.

Referring mostly to patients with what we include under the terms bundle branch block with concordant graphs and bundle branch block with discordant graphs,¹² several investigators have indicated that while the mortality seems to be high during the first year after discovery of the lesion, a remarkable diminution in the mortality rate occurs among those patients who survive this period. Referring particularly to those with the wide S wave pattern, others¹³ have remarked on the frequent

12 Sampson, J. J., and Nagle, O. E. The Prognosis of Bundle Branch Block and Other Intraventricular Conduction System Lesions, *Am J M Sc* **191** 88, 1936. Bishop, L. F., Jr., and Carden, G. A., Jr. The Prognosis of Bundle Branch Block, *Am Heart J* **17** 275, 1939. Kaplan, L. G., and Katz, L. H. Prognosis of Intraventricular Block, *ibid* **18** 145, 1939.

13 Oppenheimer, Rothschild and Mann.⁸ Von Deesten and Dolganos.⁹ Wood, Jeffers and Wolferth.¹⁰

existence of this type of electrocardiogram among patients who exhibit no clinical evidence of organic heart disease at all and who progress favorably during the period (often many years) over which they are under observation

In the studies cited in the literature the number of patients reported on was relatively small in each case, so that the need for testing the accuracy of these observations is therefore important. This we feel we have accomplished in the present study.

We believe, further, that on the basis of this study there is good justification for the subdivision into the different varieties, as defined by us, of conductive disturbances affecting the ventricular complex. They differ one from the other not only in their essential electrocardiographic configuration but also in their clinical course. It is true that between bundle branch block with concordant graphs and bundle branch block with discordant graphs, as defined by us, there is close parallelism throughout, as has been noted before,¹⁴ yet when the life expectancy curves are followed, there is sufficient difference to group the two disturbances separately.

It has long been known that patients with significant negativity of the T wave have, on the whole, a less favorable prognosis than those with the same pathologic lesion not attended by changes in the T wave. It would seem that this electrocardiographic law applies equally well when patients with two types of bundle branch block (that with concordant and that with discordant graphs) are compared with each other. There certainly is ample justification, on the basis of the clinical course alone, for placing patients with the wide S wave pattern in a separate group.

SUMMARY

Conductive disturbances affecting the ventricular complex have been variously classified and named by various authors. In the light of recent histopathologic studies in cases in which the electrocardiogram showed bundle branch defects and on the basis of the clinical behavior of patients who harbor these lesions, we suggest that conductive defects affecting the QRS complex be classified as follows: (1) bundle branch block with concordant graphs, (2) bundle branch block with discordant graphs including those cases in which the patterns resemble the electrocardiograms in the first class but without directional change in the T wave and without correlating axis deviation, (3) bundle branch block associated with the wide S wave pattern, which accounts for the increased width of the QRS complex, and (4) the type of bundle branch block

¹⁴ White, P. D., and Viko, L. E. Clinical Observations on Heart Block, *Am J M Sc* **165** 659, 1923. Graybiel, A., and Sprague, H. B. Bundle Branch Block. An Analysis of Three Hundred and Ninety-Five Cases, *ibid* **185** 395, 1933.

associated with a short PR interval (in reality a wide R wave pattern). The last is the rarest form of conduction disturbance affecting the QRS complex.

The terms complete and incomplete bundle branch block are no longer tenable so far as the electrocardiogram has been shown incapable of reflecting the extent of interruption of the bundle branches. It has also been shown that lesions affecting the conductive system similar to those causing the electrocardiographic pattern known to indicate complete bundle branch block with concordant graphs need not be associated with increased amplitude of the QRS complex or with slurring of the complexes nor need the pattern which they produce primarily conform to the classic levocardigram or dextrocardigram. The first class includes all cases in which the QRS spread measures more than 0.10 second, regardless of the amplitude of the complex or of slurring, in which the T waves in leads I and III are directed opposite to the main deflection of the QRS complex. The disturbance may assume the form of left or right bundle branch block, depending on which bundle is predominantly affected. The latter is by far the rarer of the two, and its occurrence depends in many cases on the existence of rheumatic heart disease, while hypertension and coronary disease most frequently account for the former.

In a follow-up study of a series of patients comprising 756 with bundle branch block of the concordant variety, 363 with bundle branch block of the discordant variety and 492 with the wide S wave pattern, it is shown by computation of life expectancy curves and of death rates (by actuarial methods) that the life histories of patients harboring these lesions differ one from the other. In the case of the last-named group, namely, that with the S wave pattern, the course is by far the most favorable. The highest mortality occurs during the first year after the discovery of the lesion (20 per cent). After this the annual death rate drops so that the life expectancy curve tends to parallel that of the normal population. After the S wave pattern has existed for ten years, more than a third of the patients are still alive. This is especially significant when it is remembered that the average age of the patients at the time the lesion is discovered is almost 60 years.

In the case of the group with bundle branch block with concordant graphs the highest mortality rate is also seen in the first year after the diagnosis is made, and this is the highest rate found in all the groups studied (43 per cent). As in the case of the patients with wide S wave pattern, the mortality rate drops in the succeeding years, but throughout the remaining period of study the life expectancy curve continues to drop faster than that for the normal population, so that only about 16 per cent of patients are alive ten years after the original diagnosis. Patients whose electrocardiograms show bundle branch block of the dis-

cordant type as defined by us follow a course intermediate between those of the two groups mentioned. The life expectancy curve in the first few years parallels closely that for the group with bundle branch block with concordant graphs, but after the fifth year the annual death rate drops (as compared with the first five years), so that the curve parallels that for the group with the wide S wave pattern as well as that for the normal population. In the case of the group with bundle branch block with discordant graphs 26 per cent of patients are still living ten years after the diagnosis.

Our study supports the contention that conductive defects affecting the ventricular complex have on the whole a better prognosis than was indicated by earlier studies and emphasizes the fact that prognostication must not depend on the consideration of the electrocardiographic pattern alone but that consideration must be given to the clinical condition of the patient and the functional status of the heart. The study clearly indicates that what we have termed the wide S wave pattern deserves separate classification not only on the basis of its electrocardiographic configuration but especially on the basis of the life history of patients who harbor such a disturbance.

LIFE EXPECTANCY IN CONDUCTIVE DISTURBANCES AFFECTING THE VENTRICULAR COMPLEX OF THE ELECTROCARDIOGRAM

II SPECIAL CONSIDERATION OF BUNDLE BRANCH BLOCK WITH CONCORDANT GRAPHS AND WITH DISCORDANT GRAPHS

RICHARD REESER JR, M D

Fellow in Medicine, the Mayo Foundation

FREDRICK A WILLIUS, M D

AND

THOMAS J DRY, M B

ROCHESTER, MINN

The reasons for the reclassification of bundle branch lesions, as indicated elsewhere,¹ center chiefly around the histopathologic studies of Yater and his co-workers² and of Mahaim,³ who have indicated, first, that the fibrotic changes in the conduction system which are responsible for the electrocardiographic pattern of bundle branch block are usually bilateral, though one branch is liable to show destructive effects to a more advanced degree than the other, second, that when the brunt of the destructive changes is borne by the left branch, the etiologic factor concerned is usually coronary disease or hypertension, whereas the reverse is true most generally when the heart is the seat of a chronic rheumatic lesion, third, that the amplitude of the ventricular complexes

From the Section on Cardiology, the Mayo Clinic (Drs Willius and Dry)

1 Willius, F A , Dry, T J , and Reeser, R, Jr Life Expectancy in Conductive Disturbances Affecting the Ventricular Complex of the Electrocardiogram I General Considerations of Bundle Branch Block with Concordant and with Discordant Graphs, and the Wide S Wave Pattern, Based on 1,611 Cases, Arch Int Med, this issue, p 1008

2 Yater, W M , Cornell, V H , and Claytor, T Auriculoventricular Heart Block Due to Bilateral Bundle Branch Lesions Review of the Literature and Report of Three Cases with Detailed Histopathologic Studies, Arch Int Med **57** 132 (Jan) 1936 Yater, W M Pathogenesis of Bundle Branch Block Review of the Literature, Report of Sixteen Cases with Necropsy and of Six Cases with Detailed Histologic Study of the Conduction Systems, *ibid* **62** 1 (July) 1938

3 Mahaim, I Les maladies organiques du faisceau de His-Tawara Les syndromes coronaires L'endocardite septale L'infarctus septal (etude clinique et anatomique), Paris, Masson & Cie, 1931, Nouvelles recherches sur les lesions du faisceau de His-Tawara (deuxieme memoire), le bloc de branche gauche et sa pathogenie, la sténose mitrale, Ann de med **38** 185 1935

does not seem, according to Yater's observations, to be entirely dependent on the state of the bundle branches as these are found in serial sectional studies, fourth, that slurring and notching of the ventricular complexes are not a necessary accompaniment of extreme bundle branch lesions, and, fifth, that the actual width of the QRS complexes, which varied from 0.12 to 0.16 second in the cases studied by Yater, is not dependent on the degree of destruction of the bundle branches. In 6 cases of bundle branch block reported by Yater (3 examples of predominantly right-sided lesions and 3 of predominantly left-sided lesions) the T waves were directed opposite to the main deflection of the QRS complex in leads I and III in all cases. In short, a lesion similar to that which has been regarded as responsible for the classic dextrocardiogram and the classic levocardiogram may at times result in more attenuated patterns as reflected by the electrocardiogram. Certainly the completeness or the incompleteness of the degree to which one or the other bundle has been destroyed does not seem to be reflected by the electrocardiogram and certainly not by the width of the QRS complex, as had previously been assumed, mostly on the basis of animal experiments.

We have, therefore, proposed to discard the terms "complete" and "incomplete" and include under the term "bundle branch block" with concordant graphs all cases in which the QRS complex measures more than 0.10 second, regardless of the amplitude of the ventricular complex or of slurring and of notching, and in which the T waves are directed opposite to the main deflection of the QRS complexes in leads I and III. Recognizing the universal bilaterality of these lesions, we accept the terms "right" and "left," as applied to bundle branch block as defined, to indicate more advanced damage to one or the other bundle branch.

When we exclude those electrocardiographic patterns which conform to the wide S wave pattern and the rare examples of bundle branch block associated with a short PR interval, the remainder of electrocardiograms in which the QRS interval is prolonged beyond 0.10 second differ from those showing bundle branch block with concordant graphs as defined in the preceding paragraph only in so far as the T waves are not opposite to the main deflection of the QRS complexes and in so far as they are not associated necessarily with correlating axis deviation. Cases in which these patterns, representing a less classic electrocardiographic pattern, appear we propose to designate bundle branch block with discordant graphs. It is to be stressed that hearts in cases in which electrocardiograms conformed to this pattern have thus far not been submitted to serial sectional studies.

A study of the life expectancy of patients who harbor lesions corresponding to bundle branch block with concordant graphs (right and

left) and of those with bundle branch block with discordant graphs has revealed a fairly close parallelism, yet as patients were followed from year to year after the discovery of the electrocardiographic abnormality, the latter group showed a more favorable course on the whole than the former, and for this reason, in addition to the electrocardiographic differences already enumerated, it would seem wise to separate the lesions from each other—at least until more information regarding the morphologic changes involved in their production becomes available.

ETIOLOGIC FACTORS

Age Incidence—The ages varied from 10 to 88 years in the group with bundle branch block with concordant graphs and from 15 to 84 years in that with bundle branch block with discordant graphs, the average age at the time of diagnosis being 58.6 and 58.3 years, respectively, as compared with 59.3 years in the case of the group associated with the wide S wave pattern.

Sex Incidence—Males predominated over females in the proportion of 508 to 248 in the case of bundle branch block with concordant curves and of 259 to 104 in the case of bundle branch block with discordant graphs.

Coronary Sclerosis and Hypertension—Either independently or in association with each other, these conditions were regarded as the etiologic factor in 653 of the 756 cases (86 per cent) of bundle branch block with concordant graphs and in 273 of the 363 cases (75 per cent) of bundle branch block with discordant curves.

Rheumatic Heart Disease—The diagnosis of rheumatic lesions was made in 85 cases of bundle branch block with concordant graphs and in 33 cases of bundle branch block with discordant graphs. The distribution was as follows: (1) right bundle branch block, 9 cases (with mitral stenosis in all), (2) left bundle branch block, 76 cases (with aortic disease in 50, mitral disease in 13 and both aortic and mitral disease in 12, in an additional case the condition was designated as rheumatic heart disease without further qualification), and (3) bundle branch block with discordant graphs, 33 cases. Of these, aortic disease was present in 14 and mitral disease in 10, and in 9 both aortic and mitral disease existed.

In comparison, it might be added that rheumatic lesions were associated in 44 instances with the wide S wave pattern, of which 25 were examples of mitral disease, 3 of mitral stenosis in association with aortic disease and 13 of aortic disease. It is to be noted that the incidence of aortic and mitral disease is exactly reversed in the last-named group, as compared with the other two groups.

Syphilitic Aortitis with Aortic Insufficiency—This condition occurred in 22 patients of the group with left bundle branch block with concordant graphs (and in none of the group with right bundle branch block), 7 patients with bundle branch block of the discordant variety had syphilitic aortic disease

Congenital Heart Disease—This condition was diagnosed in 1 case of right bundle branch block, in 2 cases of left bundle branch block (both concordant) and in 3 cases of bundle branch block with discordant curves. In the remaining cases, a variety of conditions existed which were not regarded as helpful in the consideration of causal factors

THE LIFE HISTORY OF PATIENTS WITH BUNDLE BRANCH BLOCK OF THE CONCORDANT AND THE DISCORDANT TYPE

The main facts relative to the fate of patients who harbor these two types of conductive disturbance, which have been considered in detail elsewhere, may be recapitulated briefly as follows. Within the first year after discovery of the disturbance there is a heavy mortality in both groups (43 and 33 per cent, respectively). In 63 per cent of the patients with bundle branch block with concordant graphs and 56 per cent of the patients with bundle branch block with discordant graphs, death is attributable directly to cardiac causes. During the years which follow, the death rates in the two groups drop considerably and for four or five years they parallel each other closely. By the sixth year, however, the death rate in the group with discordant graphs tends to parallel more closely the life expectancy curve of both the group with the wide S wave pattern and the normal population, whereas the group with bundle branch block shows a life expectancy curve which continues to drop faster than those for the normal population and for the other two groups. At the end of ten years 60 patients with concordant graphs, 37 patients with discordant graphs and 62 patients with the wide S wave pattern are still alive. After these figures are adjusted to a comparable basis by use of the life table analysis, the percentage of patients expected to live ten or more years would be 16, 26 and 38 respectively. The corresponding figure as obtained from a general life table population is 65 per cent.

Patients Who Had Died by the End of the First Year—In the group with discordant graphs 290 of the original 756 patients used in the computation of the life expectancy tables had died by the end of the first year after the discovery of the conduction defect. Since this represents the heaviest mortality during the entire period covering the survey, we analyzed the data relative to these patients, as these data would be expected to reflect the factors responsible for the high death rate. Of the 290 patients death was attributed to cardiac causes in 183 (63 per

cent) and to other causes in 27 (9 per cent). In 80 patients the cause could not be defined with certainty, though in all probability their number included several deaths due to cardiac disease.

Cardiac enlargement noted by clinical or roentgenologic methods or both was thought to be present in 241 patients (83 per cent), the number dying as a result of cardiac causes showed a particularly high percentage of cardiac enlargement (166 of 183 patients, or 91 per cent). Angina pectoris or congestive heart failure, either individually or in association with each other, occurred in 183 patients (63 per cent). The diagnosis of acute coronary occlusion was made in 22 of the number of patients dying during the first year of observation.

In the group with discordant curves evidence of gross cardiac disease was equally obvious, the number of patients dying of cardiac causes being 60 (56 per cent) of the 108 patients in this group. Twenty-one patients died of causes apparently unrelated to their cardiac condition, and in 27 instances the cause of death was unknown or uncertain.

Cardiac enlargement was noted in 81 patients (75 per cent), angina pectoris and congestive heart failure occurred either separately or in association with each other in 60 patients (56 per cent). The condition of 9 patients belonging to this group was diagnosed as acute coronary occlusion.

Patients Who Were Living Ten Years or More After the Original Diagnosis—In the group with concordant bundle branch block there were 60 and in the group with discordant bundle branch block there were 37 patients who were living ten years or more after the recognition of their electrocardiographic abnormality. An analysis of the clinical findings made at the time of the discovery of the conduction disturbance revealed the following facts. A systolic blood pressure of 170 mm. of mercury or more and/or a diastolic pressure of 100 mm. of mercury or more was noted in 22 of the 60 patients in the former group and in 10 of the 37 patients in the latter group. Cardiac enlargement was thought to be present in 36 of the former group and in 12 of the latter. A diagnosis of angina pectoris was recorded in 10 cases of concordant bundle branch block and in 3 cases of discordant bundle branch block. Congestive heart failure occurred in 1 patient belonging to the former group and in 3 patients belonging to the latter group. The relative absence of symptoms in many of these patients at the time of their original diagnosis is indicated by the fact that in the cases of only 8 patients with concordant curves and of 15 with discordant curves (to be contrasted with 42 of the 62 patients with the wide S wave pattern) was the diagnosis of coronary disease made entirely on the electrocardiographic findings.

The Clinical Status of These Patients at the Time of the Last Inquiry—Of the 60 patients with bundle branch block with concordant curves

who lived for ten years or longer, 22 had died at the time of the last report and 38 were living. Twenty-one of the 38 patients regarded themselves as being in good health, 15 were progressing favorably with restrictions and 2 regarded their health as poor in spite of restrictions. Of the 37 patients with bundle branch block of the discordant variety who lived for ten years or longer, 10 had died and 27 were living. Sixteen of the 27 patients were well, 8 were well under a restricted program and 2 were not getting along well in spite of restrictions. In 1 instance the clinical condition of the patient could not be ascertained.

THE GENERAL INCIDENCE OF CARDIAC SYMPTOMS IN THE TWO GROUPS AS A WHOLE

There are certain objections on statistical grounds to the consideration of the functional status of the heart in a heterogeneous group of patients of different ages seen over a number of years and followed for varying periods. But in so far as it was intended to draw comparisons between these groups and groups with other types of conductive disturbances (which would be subject to similar discrepancies), the incidence of congestive heart failure and of angina pectoris was computed for each group studied. It was felt that lesser degrees of coronary insufficiency and of myocardial degeneration would be extremely difficult to evaluate from the histories. Patients with paroxysmal nocturnal dyspnea were regarded as having early congestive heart failure. In the group with the concordant type of bundle branch block, angina pectoris without congestive heart failure was diagnosed in 125 cases (17 per cent) and congestive heart failure without angina pectoris in 201 cases (27 per cent). When the two conditions were considered together, it was found that in 44 per cent of patients with bundle branch block one or both conditions existed at the time the diagnosis was made. In the group with discordant curves, 48 patients (13 per cent) had angina pectoris without congestive heart failure, 81 patients (22 per cent) had congestive heart failure without angina pectoris and 37 per cent in all had either angina pectoris or congestive failure or both at the time the diagnosis was made. This is to be contrasted with 50 patients (10 per cent) with angina pectoris without congestive failure and 57 patients (12 per cent) with congestive failure without angina pectoris, or 22 per cent with one or both conditions in the group with the wide S wave pattern.

SUMMARY

The facts revealed by the detailed analysis of these types of conductive disturbance affecting the ventricular complex, namely, bundle branch block with concordant and with discordant graphs, as defined by us, emphasize again the desirability for the reclassification of such

lesions. The etiologic background from the standpoint of age and sex incidence, on the one hand, and of associated clinicopathologic findings, on the other, seems to be essentially similar in character in the two types of conduction disturbance. At the same time, the clinical course of patients whose electrocardiogram conforms to the type described as the discordant variety of bundle branch block is somewhat more favorable than is that of patients with the concordant type of bundle branch block.

Evidence of gross cardiac disease manifests itself in a high percentage of cases in the types of conductive disturbance under consideration. Our studies, however, confirm the contention expressed in some of the more recent publications dealing with this subject, that bundle branch lesions are not universally of serious prognostic significance so that in the evaluation of the cardiac status due consideration must be given to clinical data when an electrocardiographic abnormality indicative of a conductive disturbance is found to exist.

LIFE EXPECTANCY IN CONDUCTIVE DISTURBANCES AFFECTING THE VENTRICULAR COMPLEX OF THE ELECTROCARDIOGRAM

III SPECIAL CONSIDERATION OF THE WIDE S WAVE PATTERN, WITH REPORT OF THREE CASES

THOMAS J DRY, M B

FREDRICK A WILLIUS, M D

AND

RICHARD REESER JR, M D

Fellow in Medicine, the Mayo Foundation
ROCHESTER, MINN

In a previous publication¹ we have indicated that the wide S wave pattern differs from electrocardiograms produced by other forms of bundle branch defects not only in its electrocardiographic configuration but also (and this is of greater moment) in its life history. What adds to the importance of this form is not only its relative benignity but also its relative frequency. It occurred in our material as the second commonest form of conductive disturbance affecting the ventricular complex. The authenticity of its frequent occurrence can be corroborated simply by examining the electrocardiograms which have been reproduced from time to time in reports on bundle branch block already in the literature in which it will be seen repeatedly grouped along with the conventional forms of bundle branch lesions (usually the conventional type of right bundle branch block).

CHARACTERISTICS OF THE WIDE S WAVE PATTERN

The appearance of the electrocardiogram is uniformly striking, and it is seldom necessary to confirm by actual measurement that the extra width of the QRS complex is dependent solely on an S wave, broadly slurred in its most distal segment. This is best illustrated in lead I, though in many instances lead II is practically identical with lead I and

From the Section on Cardiology, the Mayo Clinic (Drs Dry and Willius)

1 Willius, F A, Dry, T J, and Reeser, R, Jr. Life Expectancy in Conductive Disturbances Affecting the Ventricular Complex of the Electrocardiogram. I. General Considerations of Bundle Branch Block with Concordant and with Discordant Graphs and the Wide S Wave Pattern, Based on 1,611 Cases, Arch Int Med, this issue, p 1008

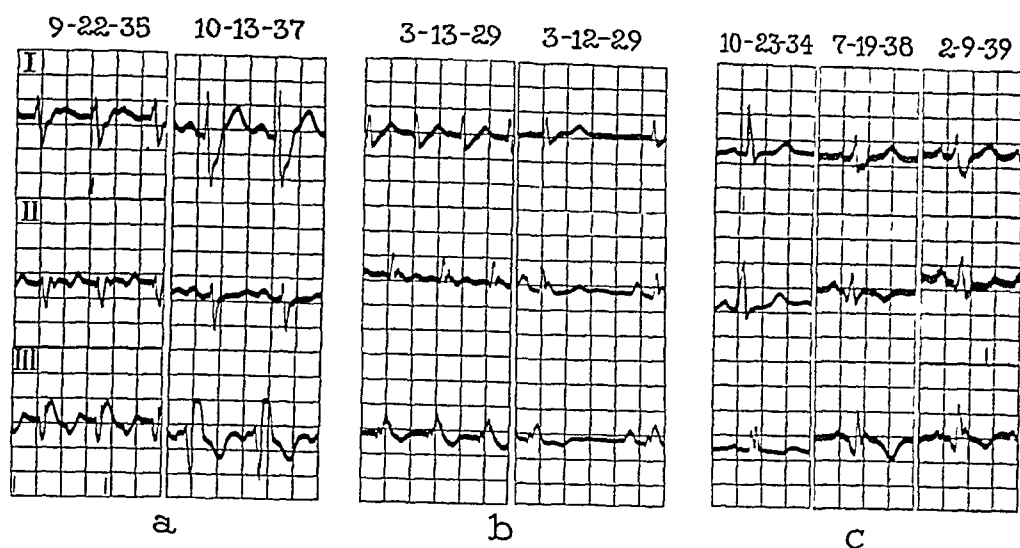


Fig 1—*a*, the wide S wave pattern associated with auricular flutter, on Sept 22, 1935, and the pattern in the same patient, with a normal rhythm, on Oct 13, 1937, illustrating the constancy in the configuration of the QRS complex, despite an ectopic rhythm *b* an example of nodal tachycardia, March 13, 1929. The QRS complex is essentially similar to that on March 12, 1929, when the rhythm was normal *c*, the effect of acute coronary occlusion on the electrocardiogram of a patient with a wide S wave pattern. The electrocardiogram taken on July 19, 1938, was preceded two weeks by typical coronary occlusion. Note the contour changes in leads II and III, which later disappear.

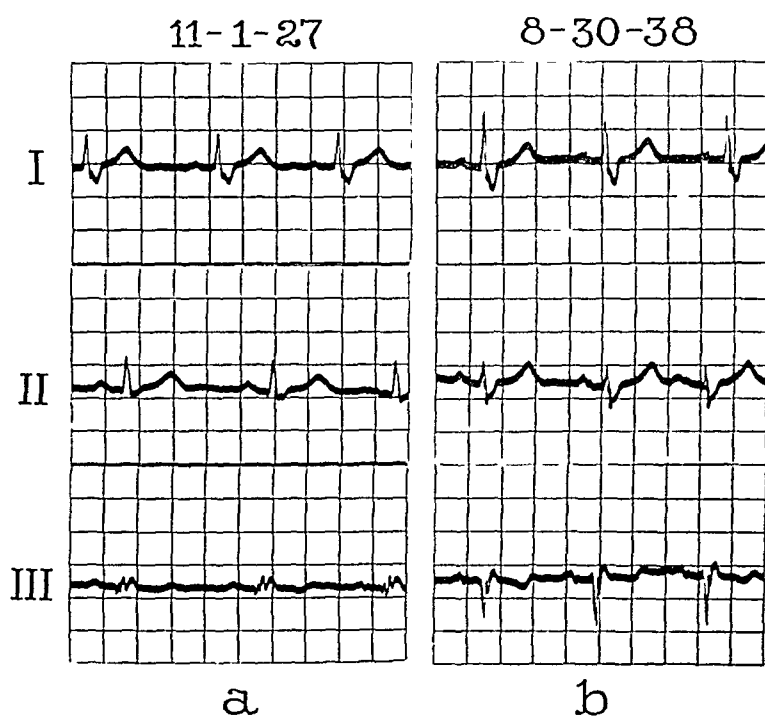


Fig 2—Two electrocardiograms recorded about eleven years apart on a patient, now 80 years old, who had no cardiac symptoms.

even lead III may show at times the essential features noted in the preceding sentence. Actually, lead III does not follow a definite pattern. Thus the QRS complex may be diphasic with the initial deflection directed either upward or downward, or the QRS complex may be monophasic. We were unable to disclose any data which would indicate important differences of prognostic significance dependent on the variation described in lead III. The T waves in lead III are inverted in the majority of instances.

The picture described in the preceding paragraph may be associated with any other recognized type of electrocardiographic abnormality. Ectopic rhythms do not alter the fundamental configuration of the QRS complex (fig 1 *a* and *b*). The amplitude of the R waves in lead I and of the S waves in lead III was noted to increase in some cases with associated hypertension as the patients were followed over a period of years. The contour of changes in the RT segment characteristic of acute coronary thrombosis resemble those seen in cases in which electrocardiograms have a normal QRS width, but the cove-shaped element has its take-off from the upstroke of the S wave rather than from the downstroke of the R wave (fig 1 *C*). The electrocardiogram may show remarkably few changes over a number of years in certain cases (fig 2).

THE PROBABLE SIGNIFICANCE OF THE WIDE S WAVE PATTERN

In so far as the wide S wave pattern is associated with an increased width of the QRS complex, it implies the existence either of a lesion interfering with conduction or perhaps of some mechanism resulting in asynchronism in the dynamic events of the two ventricles independent of a conductive disturbance.

A considerable amount of evidence supports the viewpoint that this type of electrocardiogram is the result of a disturbance of conduction affecting the right bundle branch. This evidence may be summarized briefly as follows:

1 The electrocardiographic pattern resembles that obtained in some experimental animals after destruction of the right bundle branch.²

2 The time relations of the dynamic events of the two ventricles indicate that with lesions of this kind the left ventricle contracts before the right ventricle. This has been illustrated both clinically and experimentally. Thus, as Wolferth and Margolies³ have shown, the carotid

2 Roberts, G. H., Crawford, J. H., Abramson, D. I., and Cardwell, J. C. Experimental Bundle-Branch Block in the Cat, *Am Heart J* 7: 505, 1932.

3 Wolferth, C. C., and Margolies, A. Asynchronism in Contraction of the Ventricles in the So-Called Common Type of Bundle-Branch Block. Its Bearing on the Determination of the Side of the Significant Lesion and on the Mechanism of Split First and Second Heart Sounds, *Am Heart J* 10: 425, 1935.

wave of the phlebogram (indicating contraction of the left ventricle) is inscribed before the right ventricle contracts, as indicated by sound tracings taken simultaneously with the phlebogram and the electrocardiogram. They pointed out that the first heart sound is usually split in cases of this lesion and that the second component of this split sound, which they regarded as indicative of right ventricular contraction, occurs after the inscription of the carotid wave. Braun-Menendez and Solari⁴ registered the time relations of the contractions of the two ventricles before and after cutting the right bundle branch in dogs and found that whereas before section of the bundle the two ventricles contracted simultaneously, after section the left ventricle contracted as much as 0.04 second before the right ventricle. Some of the tracings reproduced after section of the right bundle branch closely resemble the wide S wave pattern, as seen in clinical electrocardiograms.

3. Chest leads taken serially across the precordium also indicate that the left ventricle contracts before the right ventricle in cases in which there is an electrocardiogram of the wide S wave pattern. Thus, Wilson and his co-workers⁵ were able to show that when the exploring electrode is placed over the region of the right ventricle the upstroke of the R wave occurs relatively late and that when the electrode is placed over the region of the left ventricle the upstroke of the R wave is relatively early, as timed in each case against one of the conventional leads taken synchronously with the chest leads.

We are reminded of one circumstance under which an electrocardiogram indistinguishable from the wide S wave pattern occurs as a temporary event.⁶ This circumstance is the early phases of acute pulmonary embolism, when the right ventricle is suddenly subjected to a tremendously increased load, presumably as a result of spasm of the entire pulmonary arteriolar bed. Information is not available as to whether this electrocardiographic change is a fatigue phenomenon (biochemical) or one dependent on asynchronism of the two ventricles (mechanical) or, for that matter, on some other, unknown factor. In the meantime, however, we wish to record that such an electro-

4 Braun-Menendez, E, and Solari, L. A. Ventricular Asynchronism in Bundle Branch Block, *Arch Int Med* **63** 830 (May) 1939.

5 Wilson, F. N., Johnston, F. D., Hill, I. G. W., Macleod, A. G., and Barker, P. S. The Significance of Electrocardiograms Characterized by an Abnormally Long QRS Interval and by Broad S-Deflections in Lead I, *Am Heart J* **9** 459, 1934.

6 Durant, T. M., Ginsburg, I. W., and Roesler, H. Transient Bundle Block and Other Electrocardiographic Changes in Pulmonary Embolism, *Am Heart J* **17** 423, 1939.

cardiographic pattern can exist in the absence of an organic change in the conduction system. As the matter now stands, knowledge regarding the exact pathogenesis of lesions capable of producing this electrocardiographic pattern is entirely inadequate. Histopathologic studies of human hearts in which the electrocardiogram conformed to the wide S wave pattern were reported by Maham⁷ and by Evans and Turnbull.⁸ Unfortunately, in these cases there was clinical evidence of gross coronary disease which may or may not have borne any etiologic relation to the lesion responsible for the particular feature (the wide S wave of the QRS complex) of the electrocardiogram. Until further studies of well selected cases become available it might be well to maintain an unbiased viewpoint regarding its exact pathogenesis. At least our studies have shown thus far that much more frequently than in other types of bundle branch block the lesion responsible for the wide S pattern may exhibit little if any evidence of progression—indeed, to a degree singularly foreign to the vast majority of cases of coronary sclerosis in a clinically recognizable form.

In so far as direct information regarding the causation of this lesion is lacking, we may examine the indirect evidence available in our material.

ETIOLOGIC FACTORS

Age Incidence—The ages varied from 9 to 88 years. As previously noted,¹ the average age of 492 patients belonging to this group was 59.3 years at the time of the discovery of the lesion. The incidence by decades is shown in table 1, which indicates that the lesion was most frequently found in patients between the ages of 50 and 70.

Sex Incidence—Males predominate over females to an extent even greater than in the other groups studied. The ratio for males to females with the wide S wave pattern was about 4 to 1.

Coronary Sclerosis and Hypertension—A clinical diagnosis of coronary sclerosis without hypertension was made in 141 cases (29 per cent), of hypertensive heart disease without coronary sclerosis in 53 cases (11 per cent) and of hypertension and coronary sclerosis in 92 cases (19 per cent). That is, in almost 60 per cent of the cases a clinical diagnosis of coronary disease or hypertension, either independent or in association with one another, was made. In the analysis of the group, it is of interest to note that in 71 of the cases in which coronary disease was diagnosed the clinician made it clear that the diagnosis was based

7 Maham, I, cited by Wilson, F. N., Johnston, F. D., and Barker, P. S. Electrocardiograms of an Unusual Type in Right Bundle-Branch Block, *Am Heart J* 9:472, 1934.

8 Evans, W. The Newer Electrocardiogram Denoting Right Bundle-Branch Block, *Lancet* 2:1127 and 1184, 1937 (pathological report by H. M. Turnbull).

on the electrocardiographic abnormality alone and that in an additional 144 cases in which cardiac symptoms could not be elicited no specific cardiac diagnosis was denoted for indexing purposes

Rheumatic Heart Disease—A diagnosis of rheumatic heart disease was made in 44 cases (9 per cent) In 25 of these the diagnosis made was mitral stenosis and insufficiency, in 3 additional cases mitral disease was associated with aortic disease, and in 13 cases the patients were found to harbor aortic disease Other rheumatic cardiac manifestations were noted in 3 additional cases

Syphilitic Aortitis with Aortic Insufficiency—This diagnosis was made in 6 instances

TABLE 1—Age Distribution of Patients with a Wide S Wave Pattern

Age at Diagnosis, Years	Total		Males		Females	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
0-9	2	0.4	2	0.5		
10-19	2	0.4	2	0.5		
20-29	7	1.4	4	1.0	3	3.1
30-39	19	3.9	16	4.1	3	3.1
40-49	56	11.4	46	11.6	10	10.3
50-59	139	28.3	101	25.6	38	39.2
60-69	182	37.0	150	38.0	32	33.0
70-79	76	15.4	65	16.5	11	11.3
80-89	9	1.8	9	2.3		
Total	492	100	395	100	97	100
Average age	59.3 yr		60.0 yr		58.0 yr	

Congenital Heart Disease—In 6 cases the clinical findings warranted a diagnosis of congenital heart disease, and in some of these strong evidence of septal involvement existed In the remaining cases various miscellaneous conditions existed which do not merit special mention

A CONSIDERATION OF PATIENTS WHO WERE EXAMINED ON MORE THAN ONE OCCASION

An electrocardiogram was recorded on more than one occasion for 65 of the 492 patients considered in the group with the wide S wave pattern In 36 of these 65 patients the electrocardiographic pattern remained unchanged over periods as long as sixteen years after the original electrocardiogram indicating the presence of the wide S wave pattern was recorded In 12 patients additional changes which were absent on the original electrocardiogram, such as changes in the T wave prolongations of the PR interval and ectopic rhythms, were noted at a

subsequent examination, but in all these the QRS complex itself remained essentially unaltered

There were 14 patients whose cases were of special interest in so far as the wide S wave pattern developed during the period of observation. In a critical analysis of their records, it was noted that in 2 patients the wide S wave pattern developed after an acute attack of coronary thrombosis and that in 3 a wide S wave pattern developed after the patients had been known to be subjects of angina pectoris. When the anginal syndrome was first noted all three had normal electrocardiograms. One patient with essential hypertension who had had a normal electrocardiogram before an episode of congestive heart failure showed a wide S wave pattern after the episode. There was nothing, however, in the history of the remaining 8 patients to indicate why the electrocardiograms had changed from a normal pattern to one with wide S waves. Moderate hypertension existed in 3 of the 8 patients. At the completion of this study, 5 of the 8 patients were still alive (at 64, 65, 66, 67 and 71 years, respectively), and none of them presented any cardiac symptoms with the exception of 1 very obese patient who complained of dyspnea on moderate exertion. The 3 patients who had died reached the ages of 65, 73 and 78, respectively. The cause of death was stated to be cerebral hemorrhage in 2 instances and coronary thrombosis in the third, at the age of 73. The cases of the remaining 3 patients are also of special interest and require comment. Two of these represent the only examples of our series in which the disturbance indicated by the wide S wave pattern progressed into bundle branch block of the concordant variety. The third is the only instance in our series in which a patient with bundle branch block of the discordant type reverted later to a wide S wave pattern.

REPORT OF CASES

CASE 1—A woman, then 47 years old, was first seen in 1925, at which time she had exophthalmic goiter, for which thyroidectomy was done. Her electrocardiogram then showed the auricles to be fibrillating, the T wave in lead I was inverted, but the ventricular complexes were normal. Her weight then was 267 pounds (121.1 Kg). Her dyspnea was attributed to obesity and to hyperthyroidism. Two years later her electrocardiogram was essentially the same except that the T wave in lead I was now upright (fig 3). In 1929 her electrocardiogram was a typical example of a wide S wave pattern. There was no evidence of cardiac decompensation, and she was found at this visit to have diabetes. In 1934 her electrocardiogram showed bundle branch block, with the T waves diphasic in lead I. The QRS complexes measured from 0.14 to 0.16 second. She was dyspneic as before, but there was no evidence of actual congestive heart failure.

or of coronary insufficiency When she was seen a year later, she had had two cerebral vascular accidents, and she died a few months later, presumably of cardiac disease

CASE 2—The patient was first seen in 1930, when he was 59 years old This patient had had hyperthyroidism as well, for which thyroidectomy had been performed The electrocardiogram showed a wide S wave pattern No significant cardiac symptoms could be elicited, but in 1934 he returned with congestive heart failure His blood pressure, which had been normal at the first visit, was now 210 mm of mercury systolic and 104 mm diastolic The electrocardiogram showed a prolongation of the PR interval to 0.24 second, bundle branch block (the QRS interval measuring 0.12 second) and diphasic T waves in lead I He died a few months later of recurrent congestive heart failure, at the age of 63

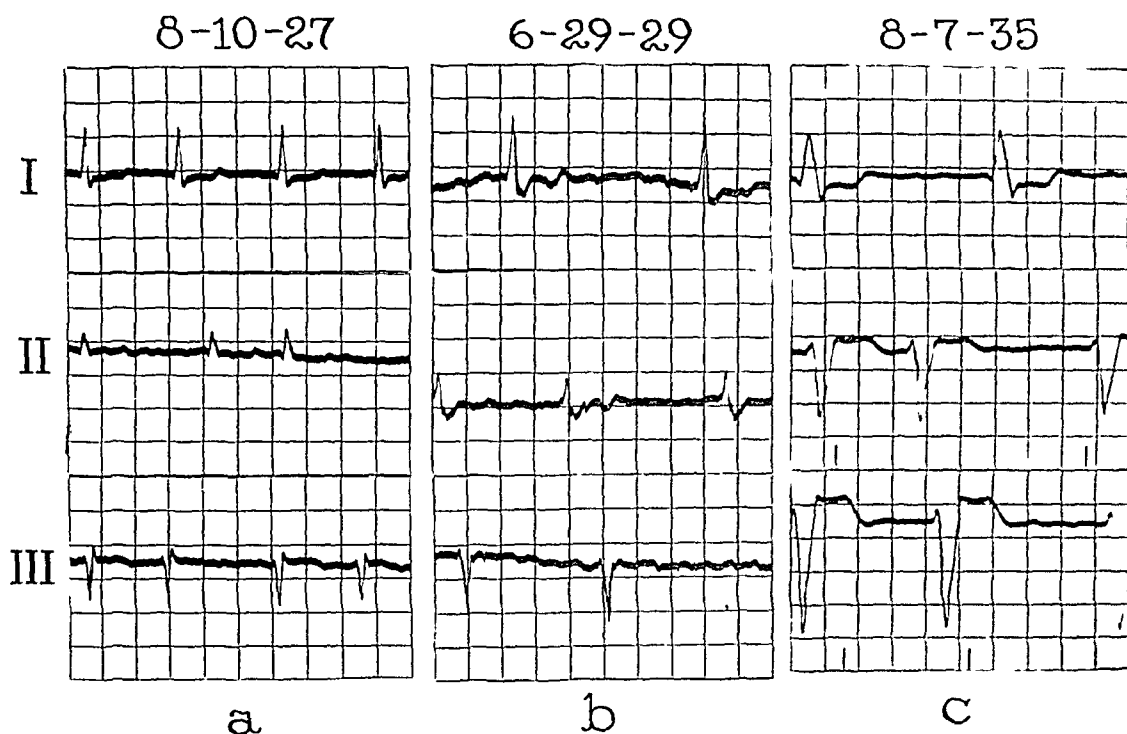


Fig 3—Three of the electrocardiograms belonging to case 1, showing that in 1927 the ventricular complexes were normal, that in 1929 a change had occurred in the ventricular complexes conforming to the wide S wave pattern and that in 1935 bundle branch block with concordant graphs existed This patient died a year later, at the age of 58, presumably of heart disease She had had at least two cerebrovascular accidents prior to death

CASE 3—A woman, then 56 years old, presented herself for examination in 1932, complaining principally of dizziness She admitted that she was dyspneic on moderate exertion An electrocardiogram then showed bundle branch block with discordant graphs (the QRS complex measuring 0.12 second), together with a 2:1 heart block Determination of the basal metabolic rate gave -21 per cent, but the classic features of myxedema were absent However, thyroid therapy was instituted, and three months later, when she was seen again, her basal metabolic rate was -3 per cent and she claimed that she was subjectively improved The electrocardiogram then showed a wide S wave pattern with a prolongation of the PR interval to 0.24 second At a recent examination this patient was found

to be in reasonably good health for her age, she is no more dyspneic on exertion now than she was in 1932, and she has taken thyroid off and on in amounts insufficient to control a true myxedematous condition. There is nothing about her present condition which suggests that she does have myxedema. The electrocardiogram is identical with the previous one, except that the PR interval now measures 0.28 second.

THE LIFE HISTORY OF PATIENTS WITH THE WIDE S WAVE PATTERN

The life expectancy curve and the death rate determinations for this group have been indicated in a previous article¹. It was shown that patients with the wide S wave pattern follow a course considerably more favorable than those with bundle branch block with concordant and with discordant curves. It was also indicated that the highest mortality occurred during the first year after the diagnosis of the lesion was made and that this was even more pronounced in cases of the other types of bundle branch block. Those who survived the first few years after the discovery of the lesion were shown to have a life expectancy curve which roughly parallels that for the normal population. This being the case, it occurred to us that a comparison of the patients who succumbed in the earlier years following the discovery of the lesion with those who were living a considerable number of years later might supply the essential factors which contributed to the high mortality of the former patients. Otherwise stated, did certain factors exist among those persons who had a poor prognosis which were absent in those whose life history continued apparently uninfluenced by the disturbance responsible for this particular electrocardiographic configuration?

We therefore reviewed the records of the 92 patients (72 men and 20 women) who died during the first year after the discovery of the electrocardiographic abnormality, as well as the records of those who were still living ten years after the original diagnosis was made.

Patients Who Had Died by the End of the First Year—This survey indicated that 26 of the 92 patients (28 per cent) died of noncardiac causes (malignant lesions, pneumonia, uremia associated with prostatic obstruction, Hodgkin's disease, postoperative peritonitis and so forth). It is to be recalled that the average age for the patient with the wide S wave pattern at the time the diagnosis was made was almost 60 years. Of the 26 patients whose death was attributable to noncardiac causes, 10 had severe hypertension (170 mm. of mercury systolic or more), in not a single patient was there congestive heart failure, but the condition of 2 was diagnosed as angina pectoris, 4 patients showed inversions of the T wave in leads II and III, and 2 showed inversions of the T wave in lead I, 5 patients had either roentgenologic or clinical evidence of cardiac hypertrophy. Of the remaining 66 patients of the number who died

within the first year after the lesion was discovered, 33 patients were known to have died as a direct result of cardiac disease. Of these 33 patients, 13 had a systolic blood pressure of 170 mm of mercury or more or a diastolic blood pressure of 100 or more, 23 patients had either congestive heart failure or angina pectoris or both, and 25 had significant electrocardiographic findings (apart from the QRS abnormality and axis deviation), consisting in 6 instances of inversion of the T wave in leads I or II or both, in 10 instances of inversion of the T wave in leads II and III, in 2 instances of inversion of the T wave in leads I, II and III, in 1 instance of prolongation of the PR interval beyond 0.20 second and in 6 instances of auricular fibrillation. Twenty-four patients had evidence of cardiac hypertrophy, either clinical or roentgenographic or both.

There remain, then, 33 patients who died during the first year for whom the cause of death was not ascertainable, but the data relevant to these patients would tend to indicate that a fairly high proportion of them succumbed to cardiac disease. Thus, 14 patients had a systolic blood pressure of 170 mm of mercury or more and/or a diastolic blood pressure of 100 mm or more, angina pectoris and/or congestive heart failure was noted in 15, 7 had significant electrocardiographic findings (apart from the QRS abnormality and axis deviation), consisting of inversion of the T wave in lead I or II or both in 2 instances, inversion of leads II and III in 4 instances and auricular fibrillation in 1 instance, 24 were thought to show cardiac enlargement, either on clinical or on roentgenologic examination or on both.

Necropsy data were available for 16 patients of the number who died during the first year of observation. The details are given in table 2, which includes data on 4 additional patients who died after the first year of observation. It will be noted again that the patients who died as a result of heart disease (10 of the 20) had abundant evidence of cardiac involvement quite apart from the electrocardiographic abnormality under discussion. Frank evidence of myocardial or coronary insufficiency was recorded in all cases, and the weights of the hearts varied from 433 to 750 Gm. With 1 notable exception (case 17), in the remaining 10 cases in which death was attributable to noncardiac disease far lesser degrees of gross cardiac involvement were exhibited both clinically and at necropsy. The average weight of the heart in these 9 cases (omitting case 17) was 409 Gm, as compared with 566 Gm in the 10 cases in which death resulted from heart disease.

In summary, then, 26 of the 92 patients who died during the first year of observation succumbed to noncardiac disease, and among these there was relatively little evidence of cardiac crippling. In contrast the

TABLE 2—Clinical and Necropsy Data for Patients with a Wide S Wave Pattern of the Electrocardiogram

Case Number	Age, Years	Sex	Cardiac Symptoms *	Blood Pressure, mm of Mercury	Other Electrocardiographic findings *	Causes of Death	Heart Weight, Gm	Coronary Sclerosis, Grade	Comment
1	56	M	0	165/90	R V P, inv T in III	Peritonitis	340	1	
2	80	M	0	112/80	Di T in II and III	Cancer	366	Not stated	
3	74	M	0	140/90	Di T in II and III	Pneumonia	380	2+	Chronic rheumatic heart disease, aortic and mitral
4†	70	M	0	144/80	Inv T in III	Pneumonia following operation on prostate gland	382	2	
5	85	F	0	200/90	R V P	Pneumonia, pernicious anemia	404	1 2	
6	87	M	0	144/90	L V P, inv T in III	Pneumonia	432	2+	
7	67	M	0	156/82	L V P, inv T in III	Intestinal hemorrhage	445	Not stated	Chronic aortic endocarditis
8	72	M	0	120/80	None	Cancer	450	2	
9	77	M	0	180/90	L V P, inv T in III	Pyelonephritis	482	2	No myofibrosis
10	64	F	Cong fail	160/70	Inv T in III	Cardiac	433	1	Mitral stenosis 2+
11	70	M	+	170/104	Inv T in III	Cardiac	455	1	Hypertension
12	68	F	+	160/150	L V P, di T in II and III	Cardiac	490	2+	
13	67	M	+	142/90	PR = 0.22 sec	Cardiac	540	1	
14	57	F	Cong fail	130/100	Aur fib	Cardiac	560	Not stated	
15	61	M	+	180/75	L V P, di T in II and III	Cardiac	560	2+	Syphilitic aortitis
16	75	M	Cong fail	112/90	L V P, di T in I	Cardiac	590	3 1	Considerable myofibrosis
17†	62	M	Cong fail	170/90	Aur fib	Exophthalmic goiter, pernicious anemia, pneumonia	621		Infarct (healing) in left ventricle
18†	57	M	Cong fail, angina	200/120	Extreme L V P	Cardiac	632	1	Considerable fibrosis
19	62	M	Angina	192/94	Inv T in II and III	Cardiac	650	1	Syphilitic aortitis, old infarct in septum
20†	53	M	Cong fail	96/78	L V P	Cardiac	750	3	Region of fibrosis in septum

* Cong fail indicates congestive failure, R V P, right ventricular preponderance, L V P, left ventricular preponderance, inv, inverted, di, diphasic, and aur fib, auricular fibrillation.
† In this case death occurred after the first year of observation.

remaining 66 patients exhibited stigmas of organic heart disease in a high percentage of cases, both clinically and at necropsy in addition to the electrocardiographic abnormality under consideration

Patients Who Were Living Ten Years or More after the Original Diagnosis—Returning now to the 62 patients who were still alive at the end of ten years after the discovery of the electrocardiographic abnormality, we find that at the time of the original examination the following data were recorded. Forty-seven were men and 15 were women. Nine patients had a systolic blood pressure of more than 170 mm of mercury and/or a diastolic blood pressure of 100 mm of mercury or more, 1 patient had had congestive heart failure, another patient gave a history of angina pectoris, 8 patients had electrocardiographic changes apart from the wide S wave pattern which required comment (6 with inversions of the T wave in leads II and III, 1 with inversion of the T wave in lead I and 1 with auricular fibrillation). Some evidence of cardiac enlargement was thought to exist in 19 patients, yet the lack of symptoms and of significant objective findings is well illustrated by the fact that in the cases of 33 of the 62 patients no specific cardiac diagnosis was made despite the electrocardiographic abnormality, and in an additional 9 instances the diagnosis of coronary disease was made on the electrocardiogram alone.

The Clinical Status of These Patients at the Last Inquiry—Of the 62 patients with the wide S wave pattern who lived ten years or longer, 15 (24 per cent) had died and 47 (76 per cent) were living. Thirty-seven of the 47 regarded themselves as in good health, 8 were well while living on a restricted program, while 2 were not progressing favorably despite restrictions.

THE GENERAL INCIDENCE OF CARDIAC SYMPTOMS IN THE GROUP AS A WHOLE

It has been shown before⁹ that, considering the group as a whole, angina pectoris and congestive heart failure, either independently or in association with each other, occurred in about 22 per cent of the patients at the time of the first examination which indicated the presence of the wide S wave pattern, and that for patients with bundle branch block with concordant graphs and bundle branch block with discordant graphs the corresponding figures were 44 and 37 per cent, respectively. Coronary occlusion was noted in 9 patients with the wide S wave pattern and in 17 and 37, respectively, of those with the discordant variety of bundle branch block and bundle branch block with concordant graphs.

⁹ Reeser, R., Jr., Willis, F. A., and Dry, T. J. Life Expectancy in Conductive Disturbances Affecting the Ventricular Complex of the Electrocardiogram. II. Special Consideration of Bundle Branch Block with Concordant Graphs and with Discordant Graphs, *Arch Int Med*, this issue, p. 1027.

COMMENT

Even though Oppenheimer and his co-workers¹⁰ drew attention, in 1925, to the favorable course which patients with the wide S wave pattern often run, few writers have since made any effort to segregate cases of this type from those of other defects of bundle branch conduction. With a few exceptions, in fact, cardiologists in general have been loath to accept any deviation from the so-called normal electrocardiographic pattern as compatible with nonprogressive heart disease. That the carefully conducted follow-up study on 64 patients, by Wood, Jeffers and Wolferth¹¹ in 1935, has similarly failed to convince some writers that patients whose electrocardiograms exhibit the wide S wave type of conductive disturbance should be considered separately from the standpoint of prognosis is evident from the fact that in reports which have been published since that time these patients have been grouped along with those showing the conventional forms of conductive defects.

Evans and Turnbull⁸ expressed the view that this type of electrocardiogram belongs to a separate group. In all the cases reported by them, however, there was obvious clinical evidence of organic heart disease, but it should be noted that the patients constituting the material for their study were from the cardiac disease department of the London Hospital and were, therefore, even less representative of a cross section of the general population than is the material in a general medical practice.

That the wide S wave pattern indicates a conductive disturbance occasioned by involvement of the right bundle branch is the view shared by most other investigators. Its exact pathogenesis, however, is but poorly understood. In the majority of cases the lesion was noted first in patients of middle life or older. The average age at the time of the discovery of the lesion differs but slightly from the average age at which are first encountered the other types (bundle branch block of either the concordant or the discordant variety) of conductive disturbance acknowledged to be due usually to coronary disease, either independently or in association with hypertension. Yet, by the same token, one encounters a strange paradox, for whereas coronary disease produces lesions which involve more predominantly the left bundle branch, all the available evidence points to the conclusion that the wide S wave pattern results from a lesion affecting the right bundle branch (predominantly, if not entirely, as in experimental lesions). In our group of cases of

10 Oppenheimer, B. S., Rothschild, M. A., and Mann, H. *Cardiographic Differentiation of a Sub-Group of Intra-Ventricular Block with Observations on the Prognosis*, *J. Clin. Investigation* **1**: 592, 1925.

11 Wood, F. C., Jeffers, W. A., and Wolferth, C. A. *Follow-Up Study of Sixty-Four Patients with a Right Bundle-Branch Conduction Defect*, *Am. Heart J.* **10**: 1056, 1935.

bundle branch block of the concordant variety (as defined by us) the ratio of cases of left bundle branch block to those of right bundle branch block was 733 to 23, a ratio in accordance with that noted by other writers. The sex incidence of the wide S wave type of conductive disturbance is the sex incidence of coronary disease. Indeed men predominate to an even greater degree than they do in cases of the other types of conductive disturbances.

The frequency with which a clinical diagnosis of hypertension and coronary disease, either independently or in association with each other, was made has been indicated. The inference, again, is that the etiologic factors concerned in most cases of this group are coronary disease and/or hypertension. There are several points to be considered, however, before such a conclusion is unequivocally accepted. 1. We are concerned with patients who are already in the arteriosclerotic age and with the age when hypertension also is common, and one may well wonder whether the presence of coronary sclerosis is merely coincidental. 2. The frequency with which the diagnosis of coronary disease is made can be materially influenced by chance electrocardiographic evidence. For our records contain many instances in which the clinician indicated that the electrocardiographic information represented the only positive finding to substantiate such a diagnosis. This was true in relatively few patients with other types of conductive disturbance affecting the ventricular complex, because other evidence of organic heart disease occurred in most of the latter.

The analysis of cases belonging to this group in which rheumatic heart lesions were found is worthy of comment. Mitral disease predominated over aortic lesions in the proportion of about 2 to 1, which is exactly the reverse of what was found in cases of both concordant and discordant bundle branch block. Here, then, is a set of circumstances not in discordance with the general viewpoint that the wide S wave pattern is the electrocardiographic manifestation of a lesion involving the right bundle branch in so far as rheumatic heart disease, and especially mitral stenosis, are far more likely to result in predominantly right-sided bundle lesions than they are in predominantly left-sided lesions. When the wide S wave pattern was encountered in relatively young persons the lesion considered to be present was invariably congenital. In some there was definite evidence of septal involvement as indicated by the presence of cyanosis. It is to be remembered in this connection that the majority of congenital lesions involving the heart cause right ventricular strain, so that here again a rational etiologic relationship between the anatomic lesion and the electrocardiographic pattern becomes evident.

The degree of coronary sclerosis in those patients whose death was a result of noncardiac causes was minimal considering that with

1 exception the patients were in the seventh, eighth or ninth decade of life. Those whose hearts showed gross evidences of disease had, without exception, the clinical evidence necessary to permit the diagnosis of such disease, and the electrocardiographic evidence could safely have been dispensed with altogether in the appraisal of their cardiac status.

One other observation seemed important to us, namely, the infrequency with which the disturbance producing the wide S wave pattern was found to progress to bundle branch block of the concordant or the discordant variety. It would seem that if the etiologic factor concerned were common to all forms of conductive disturbance, the wide S wave pattern dependent on an admittedly less serious lesion would be seen as a transitional stage to the more serious forms of conductive defect more frequently than was our experience.

SUMMARY AND CONCLUSIONS

In the present state of knowledge the wide S wave pattern is to be regarded as indicating a disturbance affecting the right bundle branch. In so far as it is most commonly seen in middle age or after and in so far as it affects men much more frequently than it does women (facts which apply equally well to other forms of conductive disturbance), one may infer that the disturbance is produced by the same process as that which is responsible for other types of conductive defect, namely, coronary sclerosis, independently or in association with hypertension. In the analysis of a large series of cases, however, certain facts are revealed which need further elucidation before they can be reconciled with such a viewpoint. Thus, if it were accepted for the moment that the ischemic effects of coronary disease constitute the underlying factor in its production, we have no information available to explain why it should be predominantly a right-sided bundle lesion when clinical experience and histopathologic studies indicate that such pathologic processes as were just suggested produce predominantly left-sided lesions. This is exemplified by the ratio of 733 examples of left bundle branch block (as defined by us) to 23 examples of right bundle branch block (both of the concordant variety), an experience in accordance with the observations of others. Among those persons with rheumatic heart disease, the valvular lesion most commonly encountered is mitral stenosis, which could be expected to cause predominantly right-sided bundle lesions, but the patients with rheumatic heart disease constitute but a small minority of the entire group of patients exhibiting this type of electrocardiogram, and if it were essentially a manifestation of rheumatic heart disease, it should be more frequently encountered not only in younger persons than is actually the case but also more frequently in patients with other stigmas of previous rheumatic infection.

In short, if we are dealing with an arteriosclerotic process, its behavior is rather out of keeping with the life history of coronary sclerosis in general, indeed, some of the hearts which were examined at necropsy showed remarkably little evidence of coronary sclerosis, considering the age of the patients concerned. If we are dealing with a rheumatic process we have to assume a minimal lesion which in the vast majority of cases has not caused any valvular lesion at all and a limited myocardial lesion at the most, and this is not in keeping with the life history or the incidence of rheumatic heart disease. We await the results of histopathologic studies in suitable cases with the hope that such studies may reveal both the distribution of the lesion and its intrinsic causation.

On the basis of clinical follow-up information, however, we are prepared to champion its classification into a separate subgroup among the conductive defects involving the ventricular complex and to regard it as a relatively benign lesion with a good prognosis when unattended by coexistent findings indicative of organic heart disease. This is especially true if the electrocardiographic abnormality has been known to be present for a year or longer.

URINARY PROTEIN PARTITIONS IN AMYLOID NEPHROSIS

SAMUEL BERG, M D *

NEWARK, N J

Urinary secretion is a mechanical process during which water and solutes are filtered from the blood through the glomerular membranes, while the plasma proteins are retained. Proteins in the urine in abnormal amounts are plasma proteins which have passed through permeable glomeruli, only insignificant amounts originate in the tubules. The mechanical process of glomerular filtration is further evidenced by the fact that protein molecules below a molecular weight of approximately 70,000 (that of hemoglobin) readily escape through the glomeruli whereas larger protein molecules are usually retained, in other words, the larger the molecular size of the urinary protein, the greater is the glomerular lesion. The albumins, being the smallest of plasma proteins, should appear earliest and in greatest amounts in the urine under abnormal renal conditions. The globulins, which are much larger, should appear only when more severe lesions are present and in lesser amounts than the albumins. Fibrinogen, the largest of all plasma proteins, should appear only in the most advanced disturbances and then only in small quantities. Determination of the protein partitions in the blood and in the urine have been made by many investigators in all types of nephropathies, with extremely conflicting results. A survey of the literature from 1882 to 1926 can be found in an article by Hiller, McIntosh and Van Slyke¹

METHOD

In an endeavor to study the physiology of protein excretion by diseased kidneys in greater detail, protein partitions were determined on individual twenty-four hour specimens of urine collected according to the schema of Mosenthal's two hour test for renal function. Simultaneous plasma protein values were obtained.

All the patients studied were men with clinically proved amyloidosis complicating tuberculosis. The daily diet contained 125 Gm of proteins and a total of 2,700 calories. Salt was considerably restricted, small amounts being used only for

* Formerly assistant attending physician, Sea View Hospital

From the Metabolic Service of Sea View Hospital, Staten Island, N Y, Dr Herman O Mosenthal, Director

1 Hiller, A, McIntosh, J F, and Van Slyke, D D. The Excretion of Albumin and Globulin in Nephritis, J Clin Investigation **24** 235-252 (June) 1927

flavoring during cooking and none at table. Fluids were limited to 15 liters per day. Blood proteins were determined either by the Howe method of protein partitioning with sodium sulfate and the micro-Kjeldahl technic, or by partitioning with ammonium sulfate and measuring the proteins quantitatively by Exton and Rose's scopometric technic.² Only the latter method was used to determine the urinary proteins.

DATA ON CASES

CASE 1—C S, aged 26, was admitted in June 1927. The diagnosis was Pott's disease with a draining sinus in the right groin and productive pulmonary lesions. The congo red test showed 100 per cent absorption several times in 1939 and 1940.

TABLE 1—*Proteins (Mg) Excreted in Urine (case 1)*

Time	Volume, Cc	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio *
8 10 a m	60	564	316	0	880	1.78
10 a m-12 m	120	588	272	0	860	2.16
12 m-2 p m	195	545	245	0	790	2.22
2-4 p m	155	457	258	0	715	1.77
4-6 p m	95	480	275	0	755	1.74
Total, day	625	2,634	1,366	0	4,000	1.92
Total, night	1,020	1,580	670	0	2,250	2.36
Total	1,645	4,214	2,036	0	6,250	1.92

Examinations made April 12, 1940

* When dividing the quantity of albumins by the quantity of globulins to determine the albumin globulin (A/G) ratio, one should remember that fibrinogen is one of the globulins and should be included with them.

TABLE 2—*Proteins (Mg) Excreted in Urine (case 2)*

Time	Volume, Cc	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8 10 a m	220	247	138	77	385	1.15
10 a m-12 m	210	200	62	0	262	3.22
12 m-2 p m	185	194	46	0	240	4.22
2-4 p m	145	340	131	36	471	2.03
4-6 p m	210	336	105	0	441	3.20
Total, day	970	1,317	482	113	1,709	2.21
Total, night	1,000	1,150	200	0	1,350	5.75
Total	1,970	2,467	682	113	3,119	3.10

Examinations made Sept. 30, 1939

CASE 2—A G, aged 30, was admitted in October 1930 and discharged in May 1940. The diagnosis was tuberculous cavities in both lungs and tuberculous laryngitis and enteritis. The congo red test has shown 100 per cent absorption six times in the past four years.

CASE 3—R O, aged 30, was admitted in November 1930 and died in October 1939. Autopsy revealed healed tuberculous lesions in the lungs, tuberculous empyema on the right side, tuberculous mesenteric lymphadenitis, tuberculous tracheitis, miliaary tuberculosis and considerable amyloidosis of the kidneys, liver, spleen and adrenal glands.

2 Exton, W. G., and Rose, A. R. Clinical Partition of Blood Proteins by Scopometry, J. A. M. A. 99:1236-1239 (Oct. 8) 1932.

CASE 4—M N, aged 57, was admitted in April 1932 and died in December 1939. The diagnosis was tuberculous cavities in both lungs, tuberculous enteritis, tuberculous epididymitis with draining sinus and amyloidosis. The congo red test has shown 100 per cent absorption five times since 1935.

TABLE 3—*Proteins (Mg) Excreted in Urine (case 3)*

Time	Volume, Cc	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8 10 a m	160	624	456	136	1,080	1 05
10 a m 12 m	110	555	425	71	980	1 12
12 m 2 p m	215	484	301	86	785	1 25
2 4 p m	200	500	350	100	850	1 11
4 6 p m	220	616	364	121	980	1 26
Total, day	905	2,779	1,896	514	4,675	1 14
Total, night	505	3,105	1,515	176	4 620	1 83
Total	1,410	5,884	3,411	690	9,295	1 43

Examinations made April 27 1939

TABLE 4—*Proteins (Mg) Excreted in Urine (case 4)*

Time	Volume, Cc	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8 10 a m	90	378	328	76	706	0 93
10 a m 12 m	110	380	340	0	720	1 12
12 m 2 p m	60	300	162	39	462	1 49
2 4 p m	60	255	198	36	453	1 09
4 6 p m	105	365	354	0	719	1 03
Total, day	425	1,678	1,382	151	3,060	1 09
Total, night	450	1 035	810	0	1,845	1 27
Total	875	2,713	2,192	151	4,905	1 11

Examinations made Oct 18 1939

TABLE 5—*Proteins (Mg) Excreted in Urine (case 5)*

Time	Volume, Cc	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8 10 a m	85	395	221	0	616	1 77
10 a m 12 m	80	384	196	0	580	1 90
12 m 2 p m	70	333	185	0	518	1 85
2 4 p m	180	315	252	0	567	1 27
4 6 p m	65	308	166	0	474	1 85
Total, day	480	1,735	1 020	0	2,755	1 70
Total, night	1,000	1,500	750	0	2,250	2 00
Total	1,480	3,235	1,770	0	5,005	1 85

Examinations made Sept 20, 1939

CASE 5—E R, aged 55, was admitted in January 1933 and died in April 1940. Autopsy revealed cavities in both lungs, Pott's disease of the dorsal portion of the spine, tuberculous enteritis, caseous mesenteric lymphadenitis and amyloidosis of the liver, spleen, kidneys, adrenal glands, stomach and intestine.

CASE 6—S S, aged 49, was admitted in January 1934. The diagnosis was tuberculous cavities in both lungs, tuberculous empyema on the right side and tuberculous osteochondritis of the first rib, with a draining sinus. The congo red test showed 100 per cent absorption in 1939.

CASE 7—A D, aged 29, was admitted in August 1935. The diagnosis was tuberculous cavities in both lungs and tuberculous prostatitis, epididymitis and vesiculitis. The congo red test showed 100 per cent absorption in 1939 and 1940.

CASE 8—E C, aged 24, was admitted in December 1935. The diagnosis was tuberculous cavities in both lungs and tuberculous empyema on the left side. The

TABLE 6—*Proteins (Mg) Excreted in Urine (case 6)*

Time	Volume, Cc	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8 10 a m	200	354	0	0	354	
10 a m 12 m	190	1,254	0	0	1,254	
12 m 2 p m	150	328	0	0	328	
2 4 p m	90	243	0	0	243	
4 6 p m	135	458	0	0	458	
Total, day	765	2,637	0	0	2,637	
Total, night	565	1,836	0	0	1,836	
Total	1,330	4,473	0	0	4,473	

Examinations made May 6, 1940

TABLE 7—*Proteins (Mg) Excreted in Urine (case 7)*

Time	Volume, Cc	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8 10 a m	180	319	212	0	531	2.36
10 a m 12 m	75	495	427	46	922	1.04
12 m 2 p m	230	504	140	0	644	.60
2 4 p m	70	189	161	17	350	1.66
4 6 p m	130	440	307	32	747	1.30
Total, day	685	1,947	1,247	95	3,194	1.55
Total, night	590	1,922	1,043	20	2,965	1.82
Total	1,275	3,869	2,290	115	6,159	1.60

Examinations made May 6, 1940

TABLE 8—*Proteins (Mg) Excreted in Urine (case 8)*

Time	Volume, Cc	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8 10 a m	70	90	0	0	90	
10 a m 12 m	100	138	0	0	138	
12 m 2 p m	105	123	0	0	123	
2 4 p m	55	80	0	0	80	
4 6 p m	60	90	0	0	90	
Total, day	390	521	0	0	521	
Total, night	900	607	0	0	607	
Total	1,290	1,128	0	0	1,128	

Examinations made April 23, 1940

congo red test showed 70 per cent absorption in 1937 and 100 per cent absorption in 1938.

CASE 9—P D, aged 37, was admitted in June 1936. The diagnosis was tuberculous cavities in both lungs and hydrothorax on the left side. The congo red test showed 90 per cent absorption in 1936, 100 per cent absorption in January

and June 1937, 90 per cent absorption in November 1937 and 65 per cent absorption in 1938 and 1939

CASE 10—J C, aged 24, was admitted in September 1936 and died in October 1939, from severe hemoptysis. The diagnosis was tuberculous cavities in both lungs, hydrothorax on the right side, tuberculous enteritis and amyloidosis.

TABLE 9—*Proteins (Mg) Excreted in Urine (case 9)*

Time	Volume, Cc	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8 10 a m	190	184	0	0	184	
10 a m 12 m	230	150	0	0	150	
12 m 2 p m	230	99	0	0	99	
2 4 p m	230	265	0	0	265	
4 6 p m	150	145	0	0	145	
Total, day	1,030	843	0	0	843	
Total, night	1,300	2,925	0	0	2,925	
Total	2,330	3,768	0	0	3,768	

Examinations made April 12, 1940

TABLE 10—*Proteins (Mg) Excreted in Urine (case 10)*

Time	Volume, Cc	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8 10 a m	160	392	288	56	680	1 13
10 a m 12 m	300	645	435	0	1 080	1 60
12 m 2 p m	285	698	399	0	1,097	1 78
2 4 p m	105	267	163	0	430	1 74
4 6 p m	120	246	162	0	408	1 47
Total, day	970	2,248	1,447	56	3,695	1 49
Total, night	1,270	1,905	825	0	2,730	2 22
Total	2,240	4,153	2,272	56	6,425	1 78

Examinations made April 21 1939

TABLE 11—*Proteins (Mg) Excreted in Urine (case 11)*

Time	Volume, Cc	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8 10 a m	100	210	198	0	408	1 03
10 a m 12 m	80	196	180	0	376	1 03
12 m 2 p m	120	294	270	0	564	1 03
2 4 p m	110	335	265	0	600	1 27
4 6 p m	105	247	236	0	483	1 03
Total, day	515	1,282	1,149	0	2,431	1 11
Total, night	800	2,160	1 640	0	2 800	1 30
Total	1 315	3,442	2,789	0	5,231	1 27

Examinations made April 30 1940

CASE 11—W L, aged 31, was admitted in January 1938. The diagnosis was tuberculous cavities in both lungs, hydrothorax on the left side, ulcerative tuberculosis of the right kidney and syphilis. The congo red test showed 100 per cent absorption.

CASE 12—N P, aged 31, was admitted in April 1938 The diagnosis was tuberculous cavities in both lungs and tuberculous laryngitis The congo red test showed 100 per cent absorption

TABLE 12—*Proteins (Mg) Excreted in Urine (case 12)*

Time	Volume, Cc	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8 10 a m	185	721	269	0	990	2.68
10 a m 12 m	165	602	231	0	833	2.68
12 m 2 p m	135	550	253	0	803	2.22
2 4 p m	110	841	72	0	913	11.69
4 6 p m	135	1,114	168	0	1,282	6.63
Total, day	730	3,828	993	0	4,821	3.85
Total, night	500	2,600	400	0	3,000	6.50
Total	1,230	6,428	1,393	0	7,821	4.61

Examinations made April 30, 1940

TABLE 13—*Proteins (Mg) Excreted in Urine (case 13)*

Time	Volume, Cc	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8-10 a m	155	511	209	0	720	2.44
10 a m 12 m	110	456	149	0	605	2.92
12 m 2 p m	125	343	107	0	450	3.20
2 4 p m	80	256	52	0	308	5.00
4 6 p m	115	350	133	0	483	2.68
Total, day	585	1,916	650	0	2,566	2.94
Total, night	680	1,700	442	0	2,142	3.81
Total	1,265	3,616	1,092	0	4,708	3.20

Examinations made April 27, 1939

TABLE 14—*Proteins (Mg) Excreted in Urine (case 14)*

Time	Volume, Cc	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8 10 a m	280	1,470	1,162	378	2,632	0.95
10 a m 12 m	200	1,280	370	240	1,650	2.10
12 m 2 p m	160	1,000	632	128	1,662	1.31
2 4 p m	230	1,300	425	174	1,725	2.01
4 6 p m	240	1,092	924	360	2,016	0.89
Total, day	1,110	6,142	3,513	1,220	9,655	1.29
Total, night	1,240	3,286	2,232	0	5,518	1.11
Total	2,350	9,428	5,745	1,220	15,171	1.35

Examinations made April 21, 1939

CASE 13—C H, aged 53, was admitted in May 1938 and died in August 1939 Autopsy revealed tuberculous cavities in both lungs, tuberculous enteritis and laryngitis, caseous mesenteric lymphadenitis and amyloidosis of the kidneys

CASE 14—S R, aged 35, was admitted in November 1938 and died in May 1939 Autopsy revealed tuberculous cavities in both lungs, tuberculous laryngitis

and enteritis, caseous mesenteric lymphadenitis, considerable amyloidosis of the spleen, pancreas, adrenal glands and kidneys but not of the liver, and terminal endocarditis and uremia

CASE 15—H S, aged 38, was admitted in March 1939 The diagnosis was tuberculous cavities in both lungs and generalized tuberculous lymphadenopathy The congo red test showed 85 per cent absorption in November 1939

CASE 16—H F, aged 41, was admitted in August 1939 The diagnosis was tuberculous cavities in both lungs, tuberculous enteritis and fistula in ano, tuberculous cervical adenitis with a draining sinus and ulcerative tuberculosis of the kidneys The congo red test showed 100 per cent absorption twice in 1939

TABLE 15—*Proteins (Mg) Excreted in Urine (case 15)*

Time	Volume, Cc	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8-10 a m	140	679	203	0	882	3.20
10 a m 12 m	Not collected					
12 m 2 p m	95	427	301	0	728	1.43
2 4 p m	85	304	104	0	408	2.92
4 6 p m	135	533	122	0	655	1.37
Total, day	455	1,943	730	0	2,673	2.66
Total, night	900	2,395	755	0	3,150	3.17
Total	1,355	4,338	1,485	0	5,823	2.92

Examinations made April 30, 1940

TABLE 16—*Proteins (Mg) Excreted in Urine (case 16)*

Time	Volume, Cc	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
8 10 a m	65	840	135	0	975	6.22
10 a m 12 m	55	616	44	0	660	14.00
12 m 2 p m	75	780	120	0	900	6.50
2 4 p m	25	302	38	0	340	7.94
4 6 p m	45	423	45	0	468	9.40
Total, day	265	2,961	382	0	3,343	7.75
Total, night	500	3,650	600	0	4,250	6.08
Total	765	6,611	982	0	7,593	6.73

Examinations made April 23, 1939

COMMENT

Blood Proteins in Amyloid Nephrosis—Most investigators have found extremely diminished values for blood proteins in cases of amyloid nephrosis accompanied by severe proteinuria Owing to the more rapid elimination of albumins than of globulins through the kidneys the former show a much greater relative decrease than the latter, with a corresponding distinct drop in the albumin-globulin ratio The variations in this series are all in the same direction but to a much less noticeable degree than in any other published study It is evident that values for blood proteins can be maintained at physiologic levels without formation of

edema, by diets supplying sufficient nitrogen in cases in which the excretion of protein in the urine is as high as 15 Gm a day. These values are shown in table 17.

Urinary Albumin-Globulin Ratios in Amyloid Nephrosis—Again most observers have stated that the urinary albumin-globulin ratio in cases of amyloid nephrosis accompanied by profuse proteinuria is lower than that associated with any other type of nephropathy, being usually under 2 and certainly under 5. In 12 of our cases the ratios were in accord with this observation, and in another (case 16) the ratio was only slightly higher. Globulins were not found in the urine in 3 cases (6, 8

TABLE 17—*Values for Blood Proteins*

Case No	Blood					Urine	
	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio	Total Protein	A/G Ratio
1	3.5	2.8	0.4	6.7	1.25	6.25	2.16
2	3.4	2.7	0.4	6.5	1.26	5.15	3.10
3	3.2	2.7	0.4	6.3	1.18	9.29	1.4
4	3.1	2.6	0.5	6.2	1.19	4.90	1.11
5	2.9	2.7	0.5	6.1	1.07	5.00	1.85
6	4.5	2.3	0.5	7.3	2.00	4.47	†
7	3.9	2.4	0.5	6.8	1.62	6.15	1.60
8	4.1	2.0	0.4	6.8	1.80	1.12	†
9	3.5	2.7	*	6.2	1.30	5.76	†
10	3.1	2.8	0.5	6.4	1.11	6.42	1.78
11	4.4	2.3	0.6	7.3	1.91	5.25	1.27
12	3.9	2.5	*	6.4	1.56	7.82	4.61
13	3.2	2.8	0.4	6.4	1.14	4.70	3.20
14	3.2	2.8	0.4	6.4	1.14	15.17	1.35
15	3.8	2.5	0.5	6.6	1.52	5.82	2.92
16	3.7	2.5	0.5	6.7	1.50	7.59	6.73

* No determinations made

† No globulin in urine

and 9) despite noticeable proteinuria in 2 of them, so that globulinuria is not necessarily associated with amyloid nephrosis.

Table 17 shows that there is no definite relationship between the albumin-globulin ratio of the blood and the albumin-globulin ratio of the urine when plasma proteins are maintained near low normal levels by adequate genesis. Several authors expressed the belief that the albumin-globulin ratio of the blood influences the proportions of albumins and globulins excreted by the kidneys, as Bing stated in 1936,³ when the relative percentage of albumin in the urine is especially low in patients with amyloidosis it is due to corresponding conditions in the blood. Contradicting this view are the data in case 11, in which the plasma proteins showed normal total and relative values, yet the urinary albumin-globulin ratio was very low.

3 Bing, J. Studies in Proteinuria, Copenhagen: Levin & Munksgaard, 1936.

Urinary Changes and Progress of Amyloid Nephrosis—Table 18 presents the data for 4 patients for whom there was an appreciable difference in time between examinations of the urine. All had rapidly progressive disease. Two of the patients (cases 4 and 5) died shortly after the last examination. This table indicates that the excretion of globulins increases at a much faster rate than that of albumins and that the urinary albumin-globulin ratio is, therefore, a better index of progress than determination of the total urinary proteins.

TABLE 18—*Instances of Changes in the Amount of Proteins (Mg) Excreted in the Urine*

	Albumin	Globulin	Fibrinogen	Total Protein	A/G Ratio
Case 1					
Oct 4, 1939	4,108	1,745	0	5,853	2.34
Six months later	4,214	2,036	0	6,250	2.07
Case 4					
April 27, 1939	1,689	853	0	2,542	1.97
Six months later	2,713	2,192	151	4,905	1.15
Case 5					
May 4, 1939	1,782	559	0	2,341	3.19
Four months later	3,235	1,770	0	5,005	1.82
Case 7					
April 23, 1939	4,688	1,167	0	5,855	4.01
Thirteen months later	3,809	2,290	115	6,159	1.61

TABLE 19—*Hourly Excretion of Urinary Proteins (Mg) **

Case No	Day	Night	Case No	Day	Night
1	400	160	9	65	209
2	180	96	10	369	195
3	467	330	11	243	271
4	306	132	12	482	214
5	275	160	13	256	153
6	264	131	14	965	394
7	361	212	15	267	225
8	52	43	16	334	303

* Day specimens were collected from 8 a.m. to 6 p.m. and night specimens from 6 p.m. to 8 a.m.

Excretion of Protein in Day and in Night Urine—It is well known that the excretion of protein in the urine per unit of time is increased after the ingestion of food and during activity, in this series the hourly output of urinary proteins during the day was greater than that during the night in 14 of the 16 cases (table 19). No reason could be found for this reversal in cases 9 and 11.

Urinary Albumin-Globulin Ratios for the Day and for the Night—Accompanying this nightly decrease in protein excretion was an increase in the urinary albumin-globulin ratio (table 20), which was due to a greater relative drop in the globulin output than in the albumin output.

Apparently, this regular decrease is due to nonfunction of the more severely affected glomeruli during the night hours when the demands on the kidneys are less.

Bearing on this phase of renal function are the observations in relation to the escape of fibrinogen. This protein which has an extremely large molecule escaped in the urine in 6 cases (tables 2, 3, 4, 7, 10 and 14), and only in cases 3 and 7 was it present in both day and night specimens. In all the other instances it was not present in the night samples, case 14 was especially noteworthy in this respect for fibrinogen was excreted in all the day specimens in amounts varying from 64 to 189 mg per hour, yet none was found in the night urine. This observation seems to support the explanation for the decrease in protein excretion, with increase in the urinary albumin-globulin ratio in the night specimens, that is the more severely affected glomeruli function only when the need for renal function is great and cease to function as the load diminishes.

TABLE 20—*Urinary A/G Ratios during Day and Night*

Case No	Day	Night	Case No	Day	Night
1	1.92	2.56	9		
2	2.21	5.75	10	1.49	2.22
3	1.14	1.83	11	1.11	1.0
4	1.09	1.27	12	3.85	6.50
5	1.70	2.00	13	2.91	.84
6			14	1.29	1.4
7	1.44	1.80	15	2.66	1.7
8			16	7.75	6.08

SUMMARY AND CONCLUSIONS

Physiologic levels of plasma proteins have been maintained by the administration of high protein diets in cases of amyloid nephrosis in which up to 15 Gm. of protein was excreted a day.

The synthesis of fibrinogen is not impaired by the presence of heavy deposits of amyloid in the liver.

The albumin-globulin ratio of the blood does not influence the albumin-globulin ratio of the urine.

The urinary proteins in cases of advanced renal amyloidosis usually but not always contain high percentages of globulins; in fact globulins may be absent entirely.

The albumin-globulin ratios of day urines were uniformly lower than the albumin-globulin ratios of night urines.

Fibrinogen is found fairly often in the urine in cases of amyloid nephrosis in which the patient excretes large proportions of globulins; and in this series it was always found during the day with customary activity, and never during the night, with rest.

Changes in the urinary albumin-globulin ratios are a better index of progress of the renal lesions in amyloid nephrosis than estimation of the total protein excretion in the urine

The hourly excretion of proteins and the urinary albumin-globulin ratios during the day are variable in patients on high protein diets under the usual daily routine in a sanatorium

In itself, determination of the urinary protein fractions is of no value in the differential diagnosis of amyloid nephrosis

From an analysis of the content of albumin, globulin and fibrinogen of the urine, it appears that all the glomeruli do not take an active part in urinary secretion throughout the day, rather that the more severely affected glomeruli function only when an increased demand is made on the kidneys and that the less severely affected glomeruli function during basal conditions

156 Roseville Avenue

Progress in Internal Medicine

DISEASES OF THE HEART

A REVIEW OF SIGNIFICANT CONTRIBUTIONS MADE DURING 1940

ASHTON GRAYBIEL, M D

WITH THE EDITORIAL ASSISTANCE OF PAUL D WHITE M D

BOSTON

The second World War is having an increasingly important effect in the field of medicine. Modern total warfare, which is directed against nations as a whole and is fought with psychologic, as well as the usual, implements of war, has created medical problems which, in magnitude and scope are without parallel. A further consequence of this conflict is the interruption or subversion of many scientific endeavors. A number of the universities in Europe have been forced to suspend all their activities and others have become geared to the war machine. This change in emphasis has not been without its effect on problems relating to the cardiovascular system. Accordingly, a section of the review is devoted to brief consideration of some of these problems.

HEART DISEASE AND THE WAR

Examination of the Heart—Inasmuch as clinical examination of the heart has attracted the attention of most physicians for many years it might seem that little could remain for further discussion in regard to the selection of military personnel. Nevertheless, a number of authors¹ have been moved to write on this subject, emphasizing those features of the cardiac examination deemed to be of chief importance in the examination of recruits and soldiers. The following summary is drawn from the sources just mentioned, from the recommendations of the subcommittee on cardiovascular disease of the National Research Council and from notes of our own.

The History In civilian practice the most important feature of the cardiac examination is a detailed and careful history. This may offer the only clues of cardiac disorder or disability and afford the only means of tracing its development. In presenting his story and describing his symptoms the patient, with rare exceptions, cooperates wholeheartedly.

From the Cardiac Clinic of the Massachusetts General Hospital

1 (a) Parkinson, J. Cardiac Examination in Wartime, *Brit M J* 1:428 1940. (b) Bourne, G. Examination of the Heart in Recruits, *ibid* 2:442 1940.

with the physician. The same degree of cooperation may not always be secured by physicians in the military services. The person examined may wish to hide certain symptoms in order to obtain admission to, or promotion in, the armed forces. Conversely, symptoms may be exaggerated or falsely said to be present if it is desired to stay out of, or be relieved from, military duty. The able examiner should, however, be able to form the questions in such a manner as to force the malingerer or falsifier to answer inconsistently.

Despite the hazard just mentioned, the history must not be neglected. The examinee should be questioned regarding the occurrence of scarlet fever, diphtheria or rheumatic fever in youth and the presence of syphilis or a nervous disorder in later years, and inquiry should be made concerning the chief cardiac symptoms of pain, dyspnea, palpitation and undue fatigability. The symptomatic aspects of neurocirculatory asthenia will be discussed in detail under that heading. If there is doubt regarding the ease with which symptoms appear during or after exercise, an exercise tolerance test may be desirable. Finally, it must be kept in mind that with a decrease in reliability of the history there is a corresponding increase in the importance of the physical examination.

Inspection. General appearance may afford useful and important information. Anxiety may be declared by flushed skin, excessive sweating and dilated pupils. In rare instances slight cyanosis may be the only clinical sign of congenital heart disease. Conspicuous pallor or clubbing of the fingers may be the result of heart disease with associated infection. Vigorous pulsation of the arteries in the neck suggests essential hypertension, hyperthyroidism, aortic regurgitation, coarctation of the aorta or anxiety. Rapid respirations are often observed in persons with neurocirculatory asthenia. Other and more obvious signs of heart disease do not require repetition.

Clinical Estimation of Heart Size. Determination of the size of the heart is the single most important procedure of the examination and the key to this determination is the location of the apex impulse. The lowest and outermost point of the impulse corresponds most nearly with the left lower border of the heart. If the heart is of normal size the left border will usually be found in the fifth intercostal space, inside the midclavicular line. If for some reason the heart is displaced upward so that the apex impulse is felt in the fourth intercostal space the normal position may be as much as 1 cm. outside the midclavicular line. If the apex impulse is felt in the sixth intercostal space it should be at least 1 cm. within the midclavicular line or cardiac enlargement may be suspected. The vigorous thrust of the overactive heart may be transmitted beyond the true apex beat, which may lead to error. Great care must be taken in these instances, and percussion may be helpful. If the heart is enlarged

the left border, determined by percussion, either will coincide with the outer margin of the apex impulse or will be lateral to it. If the heart is not enlarged, the left border, determined by percussion, either will coincide with the outer margin of the apex impulse or will be medial to it. It should be remembered that scoliosis of the spine, fibrosis of the lungs, etc., may displace the heart and the apex beat.

Rate and Rhythm If the heart rate is persistently over 100 beats a minute an explanation should be found. Such a rate does not necessarily indicate myocardial disease, as many physicians believe, but does indicate a functional disturbance which may be explained by anxiety, neurocirculatory asthenia, poor training, fever, thyrotoxicosis, etc. The underlying cause, rather than the heart rate *per se*, should be the determining factor in evaluating tachycardia.

If the heart rate is slower than 50 beats a minute the person should be exercised in order to show that a satisfactory rise in rate occurs. If the heart rate is 40 or less there is a possibility that heart block is present even though a moderate increase in rate occurs with exercise, an electrocardiogram should be taken.

If waxing and waning of the heart rate with respiration proves confusing, the rhythm should be determined while the subject holds his breath. Extrasystoles are usually of little or no significance and can be abolished with exercise. The absolute irregularity of auricular fibrillation is ordinarily readily appreciated, and the irregularity increases with exercise. Rapid (over 120 beats a minute) regular rhythms which do not change in rate with exercise require electrocardiographic study.

Sounds and Murmurs In the timing of all heart sounds and murmurs it is recommended² that the examiner fix in mind the position of the sharp second sound in the cardiac cycle as heard at the base of the heart. The examiner may then move the stethoscope toward the apex, keeping in mind the proper relation of the first and second heart sounds. Accentuation of the first sound at the mitral area may be physiologic but should draw sharp attention to the possible presence of a mitral diastolic murmur. Diminution in intensity of this sound is an unreliable sign of heart disease, unless the diminution is extreme and cannot be explained by other factors, such as a thick chest wall or emphysema. Accentuation of the second sound at the aortic area is usually associated with increased circulatory rate, with increased blood pressure in the aorta or with disease of the aorta. Accentuation of the second sound at the pulmonary area is often present in healthy young persons under the excitement of examination but may indicate pulmonary hypertension (most commonly dependent on mitral stenosis or failure of the left ventricle).

² Examination of the Heart, prepared by the Committee on Leaflets and Pamphlets of the American Heart Association, New York.

Splitting or reduplication of the first sound at the mitral area is the result of asynchronism in the early phases of contraction of the two ventricles. It is usually not a sign of heart disease, but if it is associated with splitting of the second sound as well it may be the result of block in one of the bundle branches and an electrocardiographic test may be warranted. Splitting or reduplication of the second sound at the base of the heart is the result of asynchronous closure of the pulmonary and the aortic valves. It rarely indicates heart disease but occasionally may be due to bundle branch block or to abnormally high aortic or pulmonary blood pressure.

Third heart sounds are commonly heard in healthy children or young adults and are of no pathologic significance.

The problem of the significance of heart murmurs resolves itself largely into a consideration of murmurs systolic in time, because continuous murmurs³ and, with rare exceptions, diastolic murmurs should always be regarded as being pathologically significant. In the appraisal of a murmur occurring during systole the first step is to determine the point of maximal intensity and the second to trace its transmission to other valve areas or other locations over the chest. Systolic murmurs heard maximally at the aortic area are usually significant and indicate disease of the aortic valves, disease of the aorta itself or dilation of the aorta. Systolic murmurs heard maximally at the pulmonary area are rarely of pathologic significance. They are variable in character and intensity, often becoming louder if the subject shifts from the upright to the recumbent position or disappearing if the subject inspires deeply, or exercises. Systolic murmurs heard maximally at the mitral area are often, but not always, significant, they are the most difficult to evaluate. This difficulty is readily exemplified by the gradual disappearance of murmurs which occur in nearly 10 per cent of patients after an attack of rheumatic fever. In such instances there is, undoubtedly, a long period during which the murmur appears to be innocent. Generally speaking, loud or harsh systolic murmurs heard at the mitral area which are constant in character and are not abolished with change in position of the subject, deep respiration or exercise signify deformity of the mitral valve or other disease mechanism. Such murmurs are usually widely transmitted and can be heard at the axilla or over the bases of the lungs. Loud systolic murmurs heard maximally in the third intercostal space to the left of the sternum, frequently accompanied by a thrill, suggest a congenital interventricular septal defect. Precordial systolic murmurs

3 It is important not to interpret as due to a diseased condition the continuous venous hum, heard in the neck in many healthy young persons, which is sometimes transmitted down as far as the base of the heart. This hum can be easily obliterated by light pressure over the jugular veins.

not heard maximally at the area of a valve are usually cardiorespiratory in nature and are due to movement of air in the lungs resulting from the motion of the heart. Such murmurs readily change in character or are abolished as a result of change in the position of the subject, deep inspiration or exercise.

Blood Pressure The physiologic variations in blood pressure occur so readily and are of such magnitude that normal blood pressure is difficult to define and is often a matter of individual opinion. Age, temperament, fitness and degree of anxiety are only a few of the many factors which may influence the level of blood pressure in a person at rest. In young persons there is far greater instability of both pulse rate and blood pressure than in older persons. Thus, a blood pressure of 170 mm. of mercury systolic and 80 mm. diastolic in a young, anxious recruit at the time of examination is of far less significance than a pressure of 140 mm. of mercury systolic and 95 mm. diastolic in a man of middle age. Such considerations have led many to the opinion that determinations of blood pressure should not be made routinely in the examination of recruits.

Parkinson^{1a} believes the blood pressure should be determined if the apex beat is displaced or is forceful without other cause or if the aortic second sound is accentuated. He considers that only pressures of 160 mm. of mercury systolic and 90 mm. diastolic or higher which persist after the subject has had a "fair interval" of rest should be regarded with any misgiving. Bourne,^{1b} also, calls attention to the "nervous increase" in blood pressure, presumably due chiefly to increased output, wherein the systolic pressure is temporarily raised to 170 or above but the diastolic pressure is little changed.

However, it may be desirable from a long range point of view to determine the blood pressure in every recruit, using whatever precautions are necessary to insure accuracy. Only by so doing can the comparatively large number of persons with hypertension be eliminated and the government be spared later expense of sickness benefits. The upper limit of blood pressure allowable for those under 25 years of age should be 150 mm. of mercury systolic and 80 mm. diastolic and for those over 25 years of age 140 mm. of mercury systolic and 90 mm. diastolic. Even this limit would include a number of persons in whom essential hypertension will probably develop. If higher readings are found it is certainly worth the time and effort to obtain subsequent readings after the subject has rested or to repeat the test another day. If persistently high readings are obtained in an emotionally stable person it is almost certain that arterial hypertension is present. If high readings are obtained in an emotionally unstable person his fitness for duty is open to grave doubt, many of those in whom neurocirculatory asthenia later develops will certainly be recruited from the ranks of those with persistently high blood pressure.

Electrocardiographic Tests An electrocardiographic test is rarely indicated in the routine examination of recruits for the regular service of the army or navy. In the examination of older personnel the use of the electrocardiogram in selected cases will prove of great value. In those branches of the service which demand the ultimate in physical fitness, such as aviation, electrocardiographic tests should have wide application. It must be realized, however, that the range of normal electrocardiographic findings is greater than has been appreciated and that great judgment and experience must be exercised in the interpretation of doubtful records.

Roentgenologic Studies Much the same might be said in regard to roentgen ray examination as was said previously in regard to electrocardiographic tests. In cases in which there is doubt, especially in regard to the size or shape of the heart, the use of the roentgen ray is invaluable.

Exercise Tolerance Tests There is great and widespread disagreement among competent cardiologists regarding the value of arbitrary tests designed to measure the functional capacity of the heart. The tendency is to consider such tests as measuring general physical fitness or vasomotor stability, rather than heart reserve. In most instances it is sufficient simply to inquire into the ability of the subject to perform work or exercise which will afford a rough approximation of the ease with which cardiac symptoms appear. After such inquiry, if the examiner is still in doubt, it may prove worth while actually to observe the subject's response to some exercise test. If the diagnosis of neurocirculatory asthenia is suspected an easy test is sufficient, otherwise a more strenuous test is indicated. The easier the test the more exact the criteria which may be applied, in judging response to strenuous tests such individual factors as age, weight, degree of fitness and state of training must be taken into consideration.

In England, a committee assisted by the Cardiac Society of Great Britain and Ireland, by Sir Thomas Lewis and by Dr. Paul Wood⁴ has recommended the use of the following exercise tolerance test:

- 1 The pulse rate is taken for fifteen seconds with the man standing.

- 2 The man places one foot on a chair at least fifteen inches in height, the other foot on the floor. He then raises himself until both feet are on the chair and the body is upright, then lowers himself until one foot is on the floor. This is repeated twenty times in sixty seconds. The man may use the back of the chair to steady himself when getting on and off the chair.

- 3 The pulse rate is then taken for fifteen seconds.

- 4 The man stands still, and forty-five seconds later—that is, one minute after the completion of the exercise—the pulse is taken for fifteen seconds (by which time the rate should be the same as, or lower than, the original rate), and the persistence of any dyspnea or distress noted.

4 Effort Syndrome, Brit. M. J. 2 201, 1940

The data thus ascertained are (i) the rise of pulse rate produced by the exercise, (ii) the degree of return to the constant standing pulse rate, (iii) the persistence of any dyspnea and (iv) any other signs of distress. If the man's original pulse rate is regained in sixty seconds and there is no residual dyspnea or distress, he may be regarded as possessing good exercise tolerance. If the response is unsatisfactory, the cause may lie in nervous instability or in some cardiovascular defect, and must be investigated by the appropriate examinations, to which the test must be considered as an adjunct. The test does not in itself afford conclusive evidence of these conditions or of a man's unfitness for Grade I, moreover, experience has shown that the response to this test may be rendered misleading in an otherwise healthy man by temporary toxemia—for example, the common cold—or by temporary lack of fitness following prolonged sedentary work or other causes.

Neurocirculatory Asthenia—The chief contribution to the knowledge of heart disease resulting from the American Civil War was Da Costa's recognition of the "irritable heart" of soldiers, and the chief contribution during the first World War was reemphasis of this syndrome by Sir Thomas Lewis. This disorder, which is usually termed neurocirculatory asthenia, or effort syndrome, although important in peacetime, becomes outstandingly important in wartime. Hence the present great revival of interest in the syndrome and the great desire to avoid the mistakes of the past. Because neurocirculatory asthenia is a disorder in which psychologic features predominate and somatic features are merely the expression thereof, psychiatrists have attempted to include this syndrome as part of their special domain. This challenge has been met by the cardiologists, but they are, at this time, on the defensive, having failed over a long period to make any appreciable headway in regard either to diagnosis or to treatment. The idea of collaboration between cardiologists and psychiatrists apparently has not sufficiently recommended itself.

Importance The importance of neurocirculatory asthenia in wartime is strikingly shown by Lewis's⁵ figures. He points out that during the first World War there was 1 case of sickness referable to the cardiovascular system for every 4 cases of wound. By the summer of 1918 no fewer than 70,000 soldiers in the British Army who reported sick were classed as having cardiovascular conditions, but not more than 1 in 6 suffered from disease of the heart, the rest exhibited the effort syndrome. Later on, 44,000 of them became pensioners. Lewis does not share the view held by some that the problem of effort syndrome in this war will be different from what it was in 1914. Although no figures are yet available, there is every indication that Lewis' point of view will be justified.

Etiologic Factors The fundamental cause of neurocirculatory asthenia is to be sought in the psychologic characteristics of the person which are the result of hereditary and of environmental influences. The

⁵ Lewis, T. *The Soldier's Heart and the Effort Syndrome*, ed 2, London, Shaw & Sons, Ltd, 1940.

precipitating factors may be psychologic or physical or, as is often the case, a combination of the two. The sharp rise in incidence during war-time is simply due to the greater stresses and strains attending warfare. Some persons break down under trivial stresses, and for them the margin between breaking down and being able to carry on is narrow and precarious. In this group symptoms often develop while persons are in training and long before they are ready for combat duty. But the majority breaking down, as Lewis⁵ points out, do not break on training but on duty which may involve hard physical labor, exposure to heat and cold, excessive fatigue, loss of sleep and, above all, fear, noise and the shock of battle. The British retreat from Dunkirk provides an excellent illustration.⁶ Here, a large number of men were subjected to a mass experiment in which almost all had to undergo somewhat comparable degrees of danger and strain. All must have suffered, but in the majority no serious symptoms developed and recovery from the ordeal was rapid. In a few who were more susceptible there developed neurotic or anxiety symptoms of various kinds which have necessitated long-continued treatment.

Symptoms. Breathlessness is a cardinal symptom. In fact, some believe that neurocirculatory asthenia is an anxiety state complicated by hyperventilation. However, this view is not generally held, and Sargant⁷ has recently emphasized that overventilation with its train of symptoms may properly be considered only as part of the whole syndrome. Lewis⁵ believes that the breathlessness of effort syndrome is to be distinguished from hysterical and cardiac breathlessness (and well it may be in typical examples). Hysterical breathlessness is present even at rest, while in neurocirculatory asthenia it is in response to effort or excitement. Cardiac breathlessness is also provoked by exercise but is usually deep, not shallow, and is rarely rapid.

Pain or discomfort in the chest is a frequent complaint. It is usually brought on by exercise or excitement, is commonly dull or aching and may last for hours. In some instances the pain is sharp or stabbing and may occur in various parts of the chest or in other parts of the body. In rare instances the pain radiates to the left arm, and under such circumstance it may be difficult to differentiate from the pain of angina pectoris.

Palpitation is a frequent symptom and consists chiefly in consciousness of rapid, forceful heart action. It is usually related to excitement or to exertion and is not present at rest.

Easy fatigability is often a pressing complaint, and, as Lewis points out, when it can be gaged is an excellent index of the severity of the disease.

⁶ Neurotics in the Forces, *Lancet* **2** 299, 1940.

⁷ Sargant, W. The Hyperventilation Syndrome, *Lancet* **1** 314, 1940.

Other symptoms include faintness and easy fainting, giddiness, tremor, sweating and nervousness

Therapy and Prognosis In the military services prophylaxis should be the keynote. The great importance of this is forcibly brought out by the fact that of men with neurocirculatory asthenia in the British forces sent to hospital during the first two years of the last war 43 per cent had symptoms on enlistment.⁵ Thus, the tremendous disease problem occasioned by this disorder could have been nearly halved simply by keeping such men out of the services. For those in whom the malady develops while on duty, prompt and adequate treatment will restore some to health, and the remainder should be discharged. The usual treatment consists of a careful search for all foci of infection, repeated reassurance that heart disease is not present and a restful, hygienic regimen, with carefully graded exercise. It is probable that psychotherapy should play a more important role than it does at present. While the prognosis for life is good, the prospect of a return to duty is only fair. Approximately one fourth of persons with this disease become fit again or are greatly improved, two thirds show no significant change, while the remainder become worse.

Conclusion The problem of neurocirculatory asthenia, or effort syndrome, in wartime has been clearly defined by Lewis.⁵ The first part of the problem is to keep men with this disorder out of the services. The second part is to prevent its development during the training period by a system of gradual induction into the new and rigorous conditions of army life. The third part concerns the treatment and sorting for future duty or discharge of those in whom this syndrome develops.

Injury of the Heart (Including Chemical Injury)—Chest wounds accounted for a large percentage of all injuries during the first World War,⁸ and concomitant injury to the heart and the great vessels was frequently observed. In Ryle's^{8b} series of 130 cases of penetrating wounds of the chest, the heart or the pericardium was directly involved in 7 per cent. Since the last war there have been two major advances in this regard which should prove of great value in the present conflict. The first is the improvement in operative technic and teamwork in treating injuries both of the heart and of the chest. The second is the increase in knowledge in respect to the recognition and understanding of traumatic heart disease. Prompt surgical aid may well save an appreciable number of victims of heart wound. Of particular importance is the recognition of and relief from cardiac tamponade (usually due to

8 (a) Gordon-Watson, C. Penetrating Wounds of the Chest. More Experiences in the Last War, *Lancet* 2 194, 1940. (b) Ryle, J. A. Penetrating Wounds of the Chest. Experience in the Last War, *ibid* 2 62 1940. (c) Anderson, R. G. Non-Penetrating Injuries of the Heart, *Brit M J* 2 307, 1940.

hemopericardium) Until recently it was thought that nonpenetrating chest injuries rarely affected the heart, whereas it is now known that the heart may be severely damaged even when there are no visible signs of injury over the thorax Anderson^{8c} states that during the first World War only 1 case of nonpenetrating injury to the heart was reported It is safe to say that in the present war much more attention will be given to injuries of this type

Leinoff⁹ has enumerated certain facts which help in the understanding of the mechanism involved in nonpenetrating injuries of the heart

1 The heart is not a firmly imbedded organ, but on the contrary is free and attached at its base by the large vessels This anatomical fact allows the heart to be thrown violently against the bony structures of the chest or else torn at its attachment and thus damaged

2 A hollow viscus which is distended and under pressure is more liable to be damaged by an injury than a similar organ which is relaxed During systole the heart wall is under tension and trauma at that moment may rupture or damage this organ

3 In young chests the heart actually may be compressed between the sternum and spine

4 Immediately preceding an injury the patient automatically fixes the chest in inspiration by closing the glottis and thus produces an excellent medium for the transmission of trauma from the chest wall to the internal viscera

5 Sudden increases in the intravascular pressures may force the blood back into the heart with sufficient force to damage the endocardium and other layers of the heart In the postmortem material which was studied subendocardial hemorrhages were found only in the left heart suggesting that a sudden back pressure was capable of producing this lesion

6 The amount and type of heart damage depends on the quality and quantity of the trauma

7 Trauma may be the activating factor in initiating potential disease

8 One or a combination of these factors may act to produce heart damage

He further points out that the diagnosis depends on (*a*) awareness of this clinical possibility, (*b*) history of a direct nonpenetrating injury to the chest, (*c*) a previous normal cardiovascular history, and (*d*) signs, symptoms or laboratory findings indicating damage to the heart and appearing in the great majority of the cases immediately after the injury and persisting thereafter

Asphyxiant or lung-irritant gases,¹⁰ of which phosgene is the most toxic and most important, have their most pronounced effects on the

9 Leinoff, H D Direct Nonpenetrating Injuries of the Heart, *Ann Int Med* **14** 653, 1940

10 (*a*) Medical Treatment of Gas Casualties, Air Raid Precautions Handbook no 3, London, His Majesty's Stationery Office, 1940 (*b*) Goldman, L, and Cullen, G E Some Medical Aspects of Chemical Warfare Agents, *J A M A* **114** 2200 (June 1) 1940

alveoli of the lungs The essential lesions are pulmonary edema, rupture of the alveoli with hemorrhage and thrombosis of the pulmonary vessels Pulmonary edema may result within two hours of gassing, at which time cyanosis and increased venous pressure are prominent signs and dilatation of the heart occurs So far as we are aware the cardiac embarrassment resulting from this type of injury has not been carefully studied It would appear that although the heart as a whole is affected, the chief strain is on the right ventricle, resulting in dilatation and failure The condition might properly be classed as an example of acute or subacute cor pulmonale Treatment includes venesection and administration of oxygen

Aviation and the Cardiovascular System—The evolution of man has occurred in those regions of the world with favorable climates, near or not far above the level of the sea And the countless adaptations to this environment have resulted in a harmoniously organized and integrated human being of almost infinite complexity Among the various body organs none affords a more beautiful illustration of this adaptation than does the cardiovascular system Its fundamental purpose is accomplished with such ease that in normal persons at rest not more than a tenth of the functional capacity of the circulatory system is required However, as man has sought and found methods of extending his power through mechanical means the limits of adaptation of the cardiovascular system were first reached and then exceeded Man now considers it necessary, and in the exigencies of war imperative, to subject himself to environmental conditions to which he was never adapted In the air there is the desire to ascend at such great speeds, to fly at such great heights and to turn and dive with such great force that the critical level of the human organism for such activities is often exceeded The major problems insofar as the cardiovascular system is concerned may be grouped under three main headings, namely, (1) anoxia, (2) centrifugal acceleration and (3) sudden lowering of barometric pressure

Anoxia When a person is subjected to decreasing partial pressures of oxygen in the air breathed there occurs a whole train of events which lead to collapse and death These changes begin with a decrease in the amount of oxyhemoglobin, which is associated with (or followed by) an increase in pulmonary ventilation This increase in pulmonary ventilation is largely the result of stimulation via the carotid body and leads to a lowering of the carbon dioxide tension first in the alveoli and then in the arterial blood The proportion of free carbon dioxide removed is greater than the proportion of combined carbon dioxide, and since the alkalinity of the blood is measured by the ratio of free to combined carbon dioxide, the net effect is to increase the alkalinity of the blood The final result is a significant modification of many functions and properties of the blood and, of course, of the rest of the body as well

The direct effect of anoxemia on the heart is difficult to measure. If this organ is healthy it will continue to function even after the subject has collapsed or has become unconscious. With increasing anoxemia there occurs compensatory dilatation of the coronary vessels, so that utilization of oxygen by the heart muscle, if conclusions drawn from animal experiments are valid, remains unchanged, even with extreme degrees of anoxia. Maurer¹¹ has found that in dogs there is increased lymph production during exposure to low oxygen tension. That the damage to cardiac blood capillaries was significant was shown not only by the greatly increased flow of cardiac lymph, but by the persistence of this increased flow even after long exposure to pure oxygen and by the appearance of erythrocytes in the lymph.

In normal subjects the brain suffers first, and objective signs of deterioration appear at elevations of 8,000 to 10,000 feet (2,438 to 3,048 meters). Patients with heart disease present another problem, and there is much evidence in some cases that signs or symptoms of cardiac embarrassment may result from exposure to low oxygen tensions.

The recent suggestion¹² that the normal heart is significantly affected by sudden ascents to elevations as low as 5,000 feet (1,524 meters) cannot be accepted. The only evidence given in support of this supposition is minor electrocardiographic alterations. To argue that such changes indicate myocardial impairment is wholly unwarranted and gains no support from practical experience.

Rapid ascents to altitudes of about 30,000 feet (9,144 meters) may result in unconsciousness without fainting,¹³ but if the ascent is more gradual about half of the subjects faint and the other half lose consciousness without fainting. Fainting, or circulatory collapse, may be heralded by changes in pulse rate and in blood pressure, but often these changes are not great until the moment of collapse. In many normal persons an increase in heart rate is observed at oxygen tensions corresponding to elevations of 4,000 feet (1,219 meters), and if the oxygen tension is gradually lowered until the point of collapse is reached, the final heart rate may be only 16 or 18 beats higher than the control level but sometimes is much higher. Under the same circumstances different patterns of blood pressure response may be noted. In some instances there is little change until collapse occurs, but more commonly there is a gradual rise in systolic and a fall in diastolic pressure. Sometimes there is a fall

11 Maurer, F. W. The Effects of Decreased Blood Oxygen and Increased Blood Carbon Dioxide on the Flow and Composition of Cervical and Cardiac Lymph, *Am J Physiol* **131**, 1940.

12 White, M. S. The Effect of Anoxia in High Altitude Flights on the Electrocardiogram, *J Aviation Med* **11** 166 1940.

13 Armstrong, H. G. Principles and Practice of Aviation Medicine, Baltimore: Williams & Wilkins Company, 1939.

in both systolic and diastolic pressures, which continues until the subject suddenly faints. Generally speaking, the adverse effects of asphyxia on the cardiovascular system are prevented by the administration of oxygen at elevations of 10,000 feet (3,048 meters) or higher. However, even if 100 per cent oxygen is breathed, the partial pressure of oxygen rapidly falls below normal at elevations above 33,000 feet (10,058 meters) ¹⁴

Another adverse influence on the cardiovascular system is that of centrifugal forces which may be encountered during the combat maneuvers of modern fighter aircraft ¹⁵. The effects of positive accelerations in the longitudinal axis of the body are observed most dramatically in the displacement of blood from the upper to the lower portions of the body. Forces greater than four to five times gravity acting for three seconds cannot be sustained without the occurrence of symptoms. If the force acts only for a short time, the blood supply to the eyes and then to the brain becomes deficient and there occurs a "veiling" of vision, or the "blackout". If the centrifugal force acts sufficiently long, return of venous blood to the heart becomes inadequate and complete circulatory collapse ensues. It is readily apparent that there are a number of practical problems in this connection which await solution. And these problems will become increasingly difficult in direct proportion to the increasing maneuverability of fighter aircraft.

Still another hazard which must be considered is that of aeroembolism ¹⁶. When the atmospheric pressure is suddenly decreased, as occurs during rapid ascents to high altitudes, symptoms arise as a result of the formation of gas bubbles in the body tissues and fluids. This bubble formation takes place in accordance with laws governing the solubility of gases. Blood passing through the lungs is exposed to the gases in the atmosphere, and each gas is absorbed according to its partial pressure. Relatively large amounts of nitrogen go into solution because of its high partial pressure, while oxygen and carbon dioxide are taken off in smaller amounts. The body has special transport systems for oxygen and for carbon dioxide but none for nitrogen, which is relatively inert and obeys the laws of simple solution. Now, if the atmospheric pressure is decreased the body tissues and fluids tend to give up the dissolved gases, principally nitrogen, by way of the lungs. If the decrease is sudden and of the order of half an atmosphere or more, so that the concentration of nitrogen is at least double what it should be, this gas comes out of solution and forms bubbles, which are added some oxygen, carbon dioxide and water vapor from the surrounding blood and tis-

¹⁴ Boothby, W. M., Lovelace, W. R., II, and Benson, O. O. High Altitude and Its Effect on the Human Body, *J. Aero. Sc.* 7:461, 1940. Armstrong ¹².

¹⁵ von Diringshofen, H. Medical Guide for Flying Personnel, translated by V. E. Henderson, London, Oxford University Press, 1940. Armstrong ¹².

sues Nitrogen is much more soluble in fats and oils than in water, and body fats at blood temperature dissolve five to six times as much nitrogen per unit mass as does the blood itself Because the elimination of nitrogen from the body is entirely through the blood stream those parts of the body with the poorest blood supply are the least able to lose their excess nitrogen rapidly Blood loses its excess nitrogen first and fatty tissue last There is considerable difference in opinion regarding the height of ascent before clinical symptoms appear Armstrong states that gas bubbles are found in the spinal fluid at 18,000 feet (5,486 meters), while bubbles in the blood and tissues generally have not been found below 30,000 feet (9,144 meters) He believes symptoms are rarely noted below 30,000 to 35,000 feet (9,144 to 10,668 meters) However, other observers are forming the opinion that symptoms may appear at lower altitudes than these The most dangerous symptoms occur, of course, when bubbles appear in the blood stream Aeroembolism of a cerebral artery may lead to severe disturbance of the central nervous system, while if the coronary arteries are involved heart failure may result This, then, becomes an important problem, especially in military aviation

Submarine Medicine—Many of the medical problems related to diving and to the use of submarines bear a close resemblance to those of aviation¹⁶ Most of the problems are concerned with respiration and the interchange of gases under pressure in the tissues of the body Although modern submarines are air conditioned and the percentages of oxygen and of carbon dioxide and the degree of humidity are carefully controlled, there are many occasions, such as occur during practice in the use of the rescue lung in diving and in rescue work, when the environmental conditions are abnormal Anoxia, excessive carbon dioxide and caisson disease, or bends, are some of the fields in which there is a demand for additional information The care required in the selection of personnel for submarine duty is second only to that required in the selection of pilots

PHYSIOLOGIC CONSIDERATIONS

Recent studies on the lymphatic vessels of the heart and on cardiac lymph of the dog are of considerable interest Patek¹⁷ has described in detail the three plexuses of lymphatics in the dog's heart The lymphatic capillaries in the subendocardium drain into the extensive myocardial plexus, which in turn drains into the large and small lymphatic capillaries under the epicardium From here the lymph passes into collecting trunks

16 Johnson, L W Medical Problems of Diving and Submarines, New York State J Med 40 1065, 1940

17 Patek, P R The Morphology of the Lymphatics of the Mammalian Heart, Am J Anat 64 203, 1939

which accompany the coronary vessels and eventually unite into a single vessel which drains the entire heart

Drinker and his associates¹⁸ inserted a cannula into this lymphatic vessel beyond the point of its emergence from the pericardium, near the anterior surface of the pulmonary artery. Reasons are given for believing that the lymph collected by means of this cannula represents the complete lymph flow from the heart and from no other structures. It was found that this flow is uniform while circulatory conditions remain constant but that the flow varies directly with the vigor of the heart beat. The pressure in the cardiac lymphatic was measured in 2 instances and was found to be 14.1 and 15.5 cm. of lymph, respectively. The protein in the lymph varied from 2.50 to 4.73 mg. per hundred cubic centimeters, and averaged 3.69 mg., in 18 experiments on different dogs. Cardiac lymph is a filtrate from the blood capillaries. Like lymph from all other parts of the body, it contains serum albumin and serum globulin and it clots. Drinker and associates found that if horse serum or acacia is given intravenously it is soon detectable in the cardiac lymph.

These authors point out that under normal circumstances the function of the lymphatics in the heart is obviously the same as in other parts of the body, namely, to remove the protein-containing tissue fluid from the part and, after passage through a lymph node, to return it to the circulation. The question is raised regarding the significance of the lymphatic drainage in various types of heart disease.

Maurel, Warren and Drinker¹⁹ studied the composition of mammalian pericardial fluid and reached the conclusion that it is merely slightly diluted lymph. It is in fact a filtrate from the epicardial blood capillaries, which passes not only through their endothelial walls, but through the epicardial endothelium. The average protein content of the pericardial fluid from 34 dogs was 1.7 mg. per hundred cubic centimeters, and the presence of fibrin was shown by rapid clotting immediately after removal from the animal.

SIGNS AND SYMPTOMS

Bloomfield,²⁰ in reviewing the question of dysphagia in disorders of the heart and the aorta found that this symptom may be associated with five cardiovascular lesions, namely, (1) dilatation of the left auricle

18 Drinker, C. K., Warren, M. F., Maurer, F. W., and McCarrell, J. D. The Flow, Pressure, and Composition of Cardiac Lymph, *Am. J. Physiol.* **130** 43, 1940.

19 Maurer, F. W., Warren, M. F., and Drinker, C. K. The Composition of Mammalian Pericardial and Peritoneal Fluids. Studies of Their Protein and Chloride Contents, and the Passage of Foreign Substances from the Blood Stream into These Fluids, *Am. J. Physiol.* **129** 635, 1940.

20 Bloomfield, A. L. Dysphagia with Disorders of the Heart and Great Vessels, *Am. J. M. Sc.* **200** 289, 1940.

(usually with mitral stenosis), (2) pericarditis, (3) saccular aneurysm, (4) dissecting aneurysm and (5) anomalies of the aortic arch or of the great vessels springing from it. He points out

The term "dysphagia" has been applied not only to *difficulty* in swallowing but also to *pain on swallowing* without any feeling of obstruction. Dysphagia may be due to compression or to spasm. In either case symptoms may be transient or persistent.

Marked compression of the esophagus frequently exists, however, without any interference with swallowing. This is particularly well illustrated in patients with enlargement of the left auricle, only a few of whom complain of difficulty in swallowing. Dysphagia with pericarditis is a rare event, and Bloomfield was forced to turn to older treatises for detailed accounts. It would appear that actual difficulty in swallowing probably occurs only when the esophagus is compressed by a large effusion, hence this symptom may be of practical diagnostic importance. Dysphagia is a symptom frequently associated with saccular aneurysm, particularly of the descending aorta, but even here it has often been noted that marked compression of the esophagus exists without any complaint on swallowing. Mild dysphagia is usually due to reflex esophageal spasm and is of no serious import, but severe and persistent dysphagia is often of grave prognostic importance, since it may indicate either a false aneurysm or a threatened rupture into the esophagus. In cases of dissecting aneurysm dysphagia may be a more frequent symptom than reports would indicate because it is overshadowed by other more distressing symptoms, in the differential diagnosis of coronary occlusion and dissecting aneurysm the presence of dysphagia favors the latter.

METHOD

Johnston and Kline²¹ have presented the results of tests, carried out with an acoustic model, which were designed to measure the efficiency of different types of stethoscopes in regard to both the end pieces and the tubing. They point out

The stethoscope in use is but one part of an acoustic system made up of (1) a source producing vibrations within the body which are transmitted through tissues, relatively dense as compared with air, to the wall of the chest, (2) the stethoscope, which receives vibrations at the surface of the skin and transmits them to the ear, and (3) the ear itself, which permits one to hear the vibrations as sounds.

They found that the response of any unit is much more dependent on the choice of the end piece than on the nature of the tubes, a conclusion which was supported by theoretic considerations. The most satis-

²¹ Johnston, F. D. and Kline, E. M. An Acoustical Study of the Stethoscope. Arch. Int. Med. 65:328 (Feb.) 1940.

factory bell was found to be one with as large an aperture as is practical and with a shallow air chamber, the addition of a rubber nipple over the terminal portion of a bell improved the latter's performance. In regard to the Bowles end piece, it was found that the diaphragm acts as a filter to suppress the transmission of low-pitched sounds but that the diaphragm must be stiff to be effective in this respect. The addition of a soft rubber sheath over the Bowles end piece materially improved its performance.

In conclusion Johnston and Kline point out that while some stethoscopes are better acoustic instruments than others in that they transmit more sound energy to the ear, loudness is of no importance except in regard to sounds that are so faint as to be nearly inaudible. They stress the importance, nevertheless, of having an intimate acquaintance with the kind of sound one is listening for and of being able to differentiate and interpret properly what is heard.

Segall²² has described a method for the determination of systolic and diastolic blood pressure by palpation. This is accomplished by inflating the blood pressure cuff and holding the thumb over the site of the brachial artery—firmly enough to feel vibrations which are ordinarily detected with the stethoscope, but lightly enough to escape feeling arterial pulsation. These vibrations are first felt as short sharp sensations (systolic pressure) as air is released from the cuff, they become weaker as the cuff is deflated but gradually become stronger than ever (diastolic level), after which no sensation can be felt. Segall²³ has now made over 2,000 observations comparing the palpation and the auscultation method. He has learned to expect the systolic pressure to be 10 mm. of mercury higher by palpation and the diastolic pressure 10 mm. of mercury lower by auscultation, whenever there are any differences. He points out that the method of palpation is of particular value to physicians with impaired hearing and in the determination of low blood pressures, such as obtain in shock.

CARDIAC ARRHYTHMIAS

Wiggers²⁴ has made an important contribution to the understanding of ventricular fibrillation, which, in some respects, is the most significant of all the cardiac arrhythmias. He points out that in man it is a frequent cause of death following coronary occlusion or electrocution (accidental or purposeful) and is the apparent cause of sudden death following the inhalation of chloroform, benzene, cyclopropane and other vapors. It may even prove to be a frequent cause of sudden death following injury to the chest, with or without obvious injury to the heart.

22 Segall, H. N. A Note on the Measurement of Diastolic and Systolic Blood Pressure by the Palpation of Arterial Vibrations (Sounds) over the Brachial Artery, *Canad. M. A. J.* **42** 311, 1940.

23 Segall, H. N. Personal communication to the reviewers.

24 Wiggers, C. J. The Mechanism and Nature of Ventricular Fibrillation. *Am. Heart J.* **20** 399, 1940.

Wiggers defines ventricular fibrillation as "an incoordinate type of contraction which, despite a high metabolic rate of the myocardium, produces no useful beats" He believes that recovery is rare in man even when the ventricles are "entirely normal" In records of over 400 cases of ventricular fibrillation in dogs there was only a single recovery

In a summary of the facts from various studies so far completed it is apparent that ventricular fibrillation is initiated by a highly localized stimulus This stimulus must reach a certain strength, however, or only a premature beat results Late systole constitutes the period when the ventricle is especially vulnerable to stimuli, and this has been termed the vulnerable phase of systole The capacity to fibrillate is inherent in heart muscle and does not require the sensitizing action of nerves or the presence of epinephrine or related substances, although these factors may affect the fibrillating threshold

Ventricular fibrillation is conceived as an evolution of changes from the moment of its inception until it ceases completely, which is within thirty to forty-five minutes Wiggers describes in some detail four stages of this evolution The first, or undulatory, stage lasts for only a second or two and consists of three to six undulatory contractions which have many of the earmarks of premature systoles The second stage, that of convulsive incoordination, lasts from fifteen to forty seconds and is characterized by more frequent waves of contraction which sweep over smaller sections of the ventricles, but inasmuch as not all masses contract in phase, the ventricles are pulled about in a convulsive manner The third stage, that of tremulous incoordination, lasts two to three minutes, and in this the surface of the ventricles appears to be broken up progressively into smaller and smaller independently contracting areas The fourth stage, that of atonic fibrillation, develops when the increasing anoxia caused by cessation of coronary flow results in the depression of contractile force It is characterized by the slow passage of feeble contraction wavelets a short distance over the ventricular surface

Wiggers²⁵ has clearly defined some of the requirements which must be fulfilled for successful cardiac resuscitation from ventricular fibrillation in dogs as follows

- 1 Fibrillation must cease completely in every fraction of the myocardium If even a vestige of fibrillating muscle remains, coordinate contractions never develop

- 2 Adequate pacemakers must survive in order to initiate impulses with an excitatory value which is sufficient to inaugurate coordinated contraction

25 Wiggers, C J The Physiologic Basis for Cardiac Resuscitation from Ventricular Fibrillation Method for Serial Defibrillation, *Am Heart J* 20 413, 1940

3 Not too many pacemakers—preferably one—should dominate the re-excitation of the defibrillated ventricle, for if too many act, they cause reversion to fibrillation

4 The muscle fractions which are so excited must be capable of responding with reasonably vigorous contractions, otherwise, weak, coordinated beats result, and the heart dies in a hypodynamic state or reverts to fibrillation

In regard to the first requirement, it is shown that fibrillation can be more readily abolished if, instead of a single strong countershock, three to seven weaker shocks are applied at intervals of one or two seconds. This procedure has been termed serial defibrillation. As regards the second and third difficulties, Wiggers has shown that the viability of pacemakers and of contracting myocardium can be assured by efficient cardiac massage, which restores coronary flow and relieves anoxia. The use of stimulating drugs, such as epinephrine and calcium salts, cannot be expected to benefit an anoxic mammalian heart and, after reoxygenation, usually sets up multiple pacemakers which tend to cause reversion to fibrillation.

He discusses the difficulties of meeting the aforementioned conditions in attempting to revive human fibrillating hearts and concludes

Although the problem of reviving human fibrillating hearts must not be considered hopeless, we must not yet allow ourselves and others to expect too much in a practical way from our present methods until the next fundamental forward step is taken, viz, provision of oxygen for the fibrillating ventricle by methods other than massage. Since we lack suggestions in this direction, it would seem more profitable for the present to direct research talents toward the problem of reducing the sensitivity of the ventricle to the agents which cause fibrillation, with the hope, eventually, of making the heart completely refractory to fibrillation.

CONGENITAL HEART DISEASE

Ligation of the patent ductus arteriosus (uncomplicated by infection) has now been performed in more than 25 cases,²⁶ with an operative mortality of about 7 per cent. The results have been gratifying, and not only have there been improvement in the physical condition and increase in exercise tolerance, but the likelihood of the dreaded complication bacterial endocarditis has been lessened or abolished.

Eppinger and Burwell²⁷ studied the dynamics of the circulation in patients with patent ductus arteriosus before and after closure of the ductus. They point out that when there is a shunt of blood from the

²⁶ Gross, R. E. Experiences with Surgical Treatment in Ten Cases of Patent Ductus Arteriosus, *J. A. M. A.* **115** 1257 (Oct. 12) 1940, Surgical Closure of the Patent Ductus Arteriosus, *J. Pediat.* **17** 716, 1940. Jones, J. C., Dolley, F. S., and Bullock, L. T. The Diagnosis and Surgical Therapy of Patent Ductus Arteriosus, *J. Thoracic Surg.* **9** 413, 1940.

²⁷ Eppinger, E. C., and Burwell, C. S. The Mechanical Effects of Patent Ductus Arteriosus on the Heart and Their Relation to the X-Ray Signs, *J. A. M. A.* **115** 1262 (Oct. 12) 1940.

aorta through the ductus into the pulmonary artery it simply goes through the lungs and is returned to the left side of the heart, from which it left. This shunt not only serves no useful purpose but acts to decrease the peripheral flow and place a strain on the left side of the heart. The magnitude of the shunt was such that, under the conditions of operation, from 45 to 75 per cent of the blood pumped into the aorta was short-circuited into the pulmonary artery. The authors discuss in detail the roentgenographic signs observed in patients with patent ductus arteriosus and find that while these signs may not be sufficient to establish the diagnosis definitely, they often contribute important confirmatory evidence and bear witness as to the effectiveness of therapy.

Touroff and Vesell²⁸ have reported their results in the surgical treatment of subacute bacterial endarteritis complicating patent ductus arteriosus. Of 4 patients operated on, 2 died of hemorrhage at operation, 1 died of subacute bacterial endarteritis thirty-two weeks after operation and 1 improved and was in "excellent condition" thirty-six weeks after operation. This marks the first successful treatment of subacute bacterial endarteritis by surgical means, and the achievement justifies further attempts.

RHEUMATIC HEART DISEASE

There have been a number of interesting reports²⁹ on different aspects of the rheumatic fever problem, but none are of outstanding importance.

28 Touroff, A. S. W., and Vesell, H. Experiences in the Surgical Treatment of Subacute Streptococcus Viridans Endarteritis Complicating Patent Ductus Arteriosus, *J Thoracic Surg* **10** 59, 1940, Subacute Streptococcus Viridans Endarteritis Complicating Patent Ductus Arteriosus. Recovery Following Surgical Treatment, *J A M A* **115** 1270 (Oct 12) 1940.

29 Thomson, S., and Innes, J. Haemolytic Streptococci in the Cardiac Lesions of Acute Rheumatism, *Brit M J* **2** 733, 1940. Stone, S. Treatment of Sydenham's Chorea by Fever and Vitamin B Therapy, *New England J Med* **223** 489, 1940. Hedley, O. F. Rheumatic Heart Disease in Philadelphia Hospitals. Study of 4,653 Cases of Rheumatic Heart Disease, Rheumatic Fever, Sydenham's Chorea and Subacute Bacterial Endocarditis Involving 5,921 Admissions to Philadelphia Hospitals from January 1, 1930, to December 1, 1934, III. Fatal Rheumatic Heart Disease and Subacute Bacterial Endocarditis, *Pub Health Rep* **55** 1707, 1940. Altschule, M. D., and Budnitz, E. Rheumatic Disease of the Tricuspid Valve, *Arch Path* **30** 7 (July) 1940. Stroud, W. D., and Twaddle, P. H. Fifteen Years' Observation of Children with Rheumatic Heart Disease, *J A M A* **114** 629 (Feb 24) 1940. Klein, R. I., Levinson, S. A., and Rosenblum, P. Weltmann Reaction and Sedimentation Rate During Rheumatic Fever of Childhood, *Am J Dis Child* **59** 48 (Jan) 1940. Walsh, B. J., Bland, E. F., and Jones, T. D. Pure Mitral Stenosis in Young Persons, *Arch Int Med* **65** 321 (Feb) 1940. Sosman, M. C. Subclinical Mitral Disease, *J A M A* **115** 1061 (Sept 28)

Wasson and Brown³⁰ have again reported encouraging results following inoculation of hemolytic streptococcus filtrate into patients with rheumatic fever. Five and nine-tenths per cent of the original group of 43 patients treated over a period of four years suffered attacks of acute rheumatic fever with or without carditis, whereas the two control groups observed during the same period showed an incidence of 15 and 43.4 per cent, respectively. A second group of 32 patients was immunized over a two year period. During the first year of treatment attacks of acute rheumatic fever, carditis and chorea developed in 9.4 per cent, as compared with 44 per cent in the control group. During the second year the incidence of rheumatic fever in the treated group (31 patients) was only 3.2 per cent, while in a new control group the incidence was 28 per cent. Wasson and Brown, encouraged by these results, are planning more comprehensive studies for the future. It is to be hoped that, in addition to treating larger numbers of patients, a better method of selecting controls will be used. Both the treated and the control groups should be similar in all respects, and neither patient nor parent should know whether hemolytic streptococcus filtrate or physiologic solution of sodium chloride is being given.

Coburn and Moore have further reported³¹ on the prolonged prophylactic use of sulfanilamide in treating rheumatic fever. One gram of the drug was given three times daily to large children and twice daily to small children over a period of nine months. Interestingly enough, in the 10 per cent in whom toxic effects developed, symptoms always appeared within the first two weeks. In those who tolerated the sulfanilamide during this period signs of toxicity did not develop later on. Infections of the throat caused by hemolytic streptococci developed in only 3 per cent of 184 treated children, and rheumatic fever occurred in only 1 case. In the untreated children the incidence of streptococcal infections of the throat was about 50 per cent, and the incidence of attacks of rheumatic fever was 20 per cent in one group and 30 per cent in another. These

1940 Boas, E. P., and Ellenberg, M. Rheumatic Pericarditis with Effusion Treated with Salicylates, *ibid* **115** 345 (Aug. 3) 1940. Brown, M. G., and Wolff, L. Recovery from Acute Rheumatic Fever Without Permanent Cardiac Damage, *New England J. Med.* **223** 242, 1940. Bennett, G. A., Zeller, J. W., and Bauer, W. Subcutaneous Nodules of Rheumatoid Arthritis and Rheumatic Fever, *Arch. Path.* **30** 70 (July) 1940. Swift, H. F. Rheumatic Heart Disease, Pathogenesis and Etiology in Their Relation to Therapy and Prophylaxis, *Medicine* **19** 417, 1940.

³⁰ Wasson, V. P., and Brown, E. E. Immunization Against Rheumatic Fever with Hemolytic Streptococcus Filtrate, *Am. Heart J.* **20** 1, 1940.

³¹ Coburn, A. F., and Moore, L. V. The Prophylactic Use of Sulfanilamide in Rheumatic Subjects, *M. Clin. North America* **24** 633, 1940.

results are in accord with those previously reported³² and not only suggest a means of preventing the exacerbations of rheumatic fever but afford additional evidence of the close association between this disease and streptococcic pharyngitis. If the good results obtained by Coburn and Moore and others are substantiated by further trial, the only question remaining is that of the possible harmful effects of prolonged administration of sulfanilamide. The answer to this question will probably appear as a corollary to the answer to the main problem.

BACTERIAL ENDOCARDITIS

Chemotherapy alone or in combination with some other therapeutic measure³³ has now been tried in a large number of cases of subacute bacterial endocarditis. The results, in our opinion, are definitely encouraging, in view of the heretofore hopeless prognosis. Lichtman and Bierman³⁴ have reviewed the published reports in an effort to arrive at a tentative conclusion as to which method of treatment at present offers the greatest hope for recovery. They have analyzed the cases of 287 adequately treated patients. Of a total of 198 patients treated with sulfanilamide and its derivatives, recovery occurred in 12, or 6 per cent. Although most of the 198 patients received sulfanilamide, the preference at this time is for sulfapyridine (2-[paraaminobenzenesulfonamido]pyridine). Favorable results have not been obtained with sulfathiazole (2-[paraaminobenzene]thiazole) when the endocarditis has been due to *Streptococcus viridans*. Of a total of 43 patients receiving chemotherapy and heparin, 5, or 11.5 per cent, have recovered. Of 25 patients subjected to chemotherapy and hyperthermia, 4, or 16 per cent, have recovered, and in a series of 21 patients who were given intravenous injections of typhoid-paratyphoid vaccine to induce pyrexia, 5, or 25 per cent, recovered. Among 6 additional patients receiving chemotherapy and radiotherapy there were no recoveries. Lichtman and Bierman conclude that the incidence of recovery from subacute bacterial endocarditis when chemotherapy is combined with additional forms of treatment, such as use of heparin and induction of hyperthermia, is twice as good as when sulfanilamide or one of its derivatives is employed alone. It would also appear that the combined use of intravenous injections of typhoid-paratyphoid vaccine and chemotherapy deserves especial mention and further trial.

32 Thomas, C. B., and France, R. A Preliminary Report of the Prophylactic Use of Sulfanilamide in Patients Susceptible to Rheumatic Fever, *Bull. Johns Hopkins Hosp.* **64**: 67, 1939.

33 Bierman, W., and Baehr, G. The Use of Physically Induced Pyrexia and Chemotherapy in the Treatment of Subacute Bacterial Endocarditis, *J. A. M. A.* **116**: 292 (Jan. 25) 1941.

34 Lichtman, S. S., and Bierman, W. The Treatment of Subacute Bacterial Endocarditis. Present Status, *J. A. M. A.* **116**: 286 (Jan. 25) 1941.

Osgood³⁵ also reports a few favorable results following the intensive use of neoarsphenamine, but others have not as yet reported similar success

With regard to chemotherapy for subacute bacterial endocarditis, it appears that if the initial response to the drug is not favorable the likelihood of cure is negligible. Exceptionally, it has been noted that if the response to sulfapyridine is poor or if so-called sulfapyridine fastness results, a change to sulfanilamide or sulfathiazole may be worth while. This great variability in response, wherein the symptoms and fever disappear and the blood stream is sterilized in one case and not in another, suggests that the various strains of *Str. viridans* respond differently to the drugs used. This is illustrated nicely by the observations of Swain³⁶. He compared the action of these drugs clinically with that on the same organism in vitro. In 2 cases in which response was poor or there was none at all the streptococci obtained on culture grew freely in broth containing the drugs. In 2 other cases in which there was a favorable response to treatment, the growth of streptococci obtained on culture was inhibited by low concentration of the drug. Here, obviously, is a good line of attack. It not only provides a plausible explanation for the small number of cures but suggests the necessity for the proper selection of cases. If most strains of *Str. viridans* are resistant to the drugs known at present it should encourage the preparation of related compounds which may prove more effective.

Bacterial endocarditis complicating syphilitic disease of the aortic valve has heretofore been regarded as a rare anomaly. It is, therefore, somewhat surprising to have for review three papers published on this subject during the past year³⁷. It would appear that bacterial endocarditis may be associated with syphilitic disease of the aorta alone or with syphilitic involvement of the cusps and commissures of the aortic valves. The diagnosis is usually difficult but may be suspected when, in the presence of syphilitic aortic insufficiency, there occur the intermittent fever and the secondary anemia which so often characterize subacute bacterial endocarditis.

EXPERIMENTAL RENAL HYPERTENSION

It has been increasingly difficult to keep abreast of the many investigations dealing with experimental arterial hypertension, and reference

³⁵ Osgood, E. E. Personal communication to the reviewers

³⁶ Swain, R. H. A. Strain Variations in the Resistance of *Streptococcus Viridans* to Sulphonamide Compounds, *Brit. M. J.* **1** 722, 1940

³⁷ Rosenberg, D. H. Bacterial Endocarditis and Syphilis of the Aortic Valve, *Arch. Int. Med.* **66** 441 (Aug.) 1940. Boyd, C. H. Bacterial Endocarditis and Syphilitic Heart Disease, *Rhode Island M. J.* **23** 47, 1940. Braunstein, A. L., and Townsend, S. R. Bacterial Endocarditis Superimposed on Syphilitic Aortic Valvulitis, *Arch. Int. Med.* **65** 957 (May) 1940

should be made to recent reviews³⁸ for comprehensive and detailed reports. The investigations so far have conclusively demonstrated a direct relationship between renal ischemia and hypertension in laboratory animals. Furthermore, there is growing evidence of similarity between this form of experimental hypertension and essential hypertension. And, finally, the culmination of this work is seen in the carefully worded, yet none the less dramatic, announcements of the successful treatment of experimental hypertension in animals and of hypertension in man by the use of kidney extracts.

The Mechanism of Renal Hypertension—Investigations continue to center around renin, the protein-like pressor substance of the kidney.³⁹ It has now been shown that renin may be produced by the completely, as well as the partially, ischemic kidney.⁴⁰ The experiments of Kohlstaedt and Page⁴¹ provide a clue to the reason clamping the renal artery is effective in producing hypertension. Isolated dog's kidneys were perfused with defibrinated blood under various hemodynamic conditions. Venous blood from the perfused kidney was tested for renin by addition of renin activator and observation of its pressor effect on the vessels of the isolated rabbit's ear. It was found that renin was not secreted by the kidney during normal pulsate perfusion but that it was secreted when the pulse pressure was reduced by partially clamping the renal

38 Blalock, A. Experimental Hypertension, *Physiol Rev* **20** 159, 1940. Page, I. H. Newer Aspects of Experimental Hypertension, Publication 13, American Association for the Advancement of Science, 1940, p. 239. Goldblatt, H. Studies on Experimental Hypertension. XII. The Experimental Production and Pathogenesis of Hypertension Due to Renal Ischemia, *Am J Clin Path* **10** 40, 1940.

39 Battro, A., Braun-Menendez, E., Lanari, A., and Leloir, L. F. Acción presora en el hombre de la renina y de la hipertensina, *Rev Soc argent de biol* **16** 376, 1940. Blalock, A., Levy, S. E., and Cressman, R. D. Experimental Hypertension. The Effects of Unilateral Renal Ischemia Combined with Intestinal Ischemia on the Arterial Blood Pressure, *J Exper Med* **69** 833, 1939. Taggart, J., and Drury, D. R. The Action of Renin on Rabbits with Renal Hypertension, *ibid* **71** 857, 1940. Corcoran, A. C., and Page, I. H. The Effects of Angiotonin on Renal Blood Flow and Glomerular Filtration, *Am J Physiol* **130** 335, 1940. Gerbi, C., Rubenstein, B. B., and Goldblatt, H. Studies on Experimental Hypertension. X. The Oxygen Consumption of the Ischemic Kidney, *J Exper Med* **71** 71, 1940.

40 Taquini, A. C. The Production of a Pressor Substance by the Totally Ischemic Kidney, *Am Heart J* **19** 513, 1940. Prinzmetal, M., Lewis, H. A., and Leo, S. D. The Etiology of Hypertension Due to Complete Renal Ischemia, *J Exper Med* **72** 763, 1940. Leo, S. D., Prinzmetal, M., and Lewis, H. A. Observations upon the Pressor Substance Causing the Rise in Blood Pressure Following the Termination of Temporary Complete Renal Ischemia, *Am J Physiol* **131** 18, 1940.

41 Kohlstaedt, K. G., and Page, I. H. Liberation of Renin by Perfusion of Kidneys Following Reduction of Pulse Pressure, *J Exper Med* **72** 201, 1940.

artery Under these conditions the secretion of renin was not prevented by increasing the rate of flow or pressure of the perfusate The authors concluded that the change from normal pulsate to continuous flow, following the clamping of the renal artery, leads to edema and anoxia of the cells of the tubules Thus, in turn, increases permeability of the cellular membrane and allows the liberation of the large renin molecule

Apparently, renin requires the presence of another substance, normally present in plasma, before its full pressor effect is manifested Muñoz and his associates⁴² regard renin as an enzyme which acts on a blood globulin, hypertensin precursor, and gives rise to a substance, hypertensin, which has a direct vasoconstrictor action They also describe another enzyme, hypertensinase, which destroys hypertensin and is present in blood and tissues Page and his associates,⁴³ also, believe that renin is an enzyme which reacts with renin activator to produce a pressor substance, angiotonin Angiotonin does not exert its vasoconstrictor effect in the absence of a substance contained in red blood cells, which has been termed angiotonin activator Repeated injections of angiotonin lead to gradual lessening of the pressor response, which, Page believes, is due not only to exhaustion of the activating substance but to the development of inhibitor substances That these inhibitors originate in large part in the kidneys is apparently shown by the increased sensitivity to angiotonin following bilateral nephrectomy

At this point it is of interest to mention the results of some experiments carried out by Dock⁴⁴ He found that on pithing the central nervous system of rabbits with renal hypertension there is a rapid fall of blood pressure to as low a level as that of normal controls A rise in arterial pressure was easily evoked with epinephrine or with renin From this it is argued that renin must, therefore, differ from the humoral agent causing chronic hypertension Furthermore, it was found that pithed hypertensive animals are much more sensitive than pithed control animals, although in the former sensitivity was lost within thirty hours after removal of the kidney which had caused the hypertension Dock concludes that the nervous system is as important in maintaining hypertension as it is in maintaining normal pressure levels and that the humoral

⁴² Muñoz, J. M., Braun-Menendez, E., Fasciolo, J. C., and Leloir, L. F. The Mechanism of Renal Hypertension, *Am J M Sc* **200** 608, 1940

⁴³ Page, I. H., and Helmer, O. M. Angiotonin-Activator, Renin- and Angiotonin-Inhibitor, and the Mechanism of Angiotonin Tachyphylaxis in Normal, Hypertensive, and Nephrectomized Animals, *J Exper Med* **71** 495, 1940 Kohlstaedt, K. G., Page, I. H., and Helmer, O. M. The Activation of Renin by Blood, *Am Heart J* **19** 92, 1940 Page, I. H., and Helmer, O. M. A Crystalline Pressor Substance (Angiotonin) Resulting from the Reaction Between Renin and Renin-Activator, *J Exper Med* **71** 29, 1940

⁴⁴ Dock, W. Vasoconstriction in Renal Hypertension Abolished by Pithing, *Am J Physiol* **130** 1, 1940

agent in renal hypertension may act by increasing the sensitivity to epinephrine and to stimuli of vasomotor nerves and by modifying the "set of the vasomotor mechanism," just as substances from inflamed or necrotic tissue modify the set of the heat-regulating center. Thus, both a humoral and a nervous mechanism are postulated as causative and maintaining factors in renal hypertension.

That the normal kidney in some manner limits the pressor effect in experimental hypertension has been shown by several investigators. More recently it has been shown that extracts of kidney (and of muscle) reduce the blood pressure in experimental renal hypertension and in essential and malignant hypertension in man.

Harrison, Grollman and Williams⁴⁵ have prepared a kidney extract which is effective in lowering the blood pressure in hypertensive rats, dogs and human subjects. The extract is prepared only with great difficulty, and, though the chemical nature of the active principle is unknown, it has certain unique properties which differentiate it from various depressor tissue extractives previously described. The extract was given orally or parenterally to a few patients with advanced and severe hypertension. In most of the subjects there was a decline in the blood pressure and subjective improvement, but the authors prefer to regard the studies on patients as inconclusive and still in the experimental stage.

Page and his associates⁴⁶ write with greater assurance. They prepared extracts from fresh kidneys and other tissues, chiefly muscle. Each of the 8 patients who received these extracts responded with "a sharp prolonged fall in arterial pressure," whether the hypertension was malignant or essential. Associated with the fall in blood pressure was marked improvement. Three to five days after the treatment was discontinued the blood pressure tended to rise again. Page and associates point out that there is little likelihood that the fall in blood pressure could be due to any of the known depressor substances, for three reasons. First, the fall occurs slowly—over a period of twelve to forty-eight hours—depending on dosage. Second, all crystalloidal substances would have been lost during dialysis, for the inhibitor is nondialyzable. Third, the reduction

45 Harrison, T. R., Grollman, A., and Williams, J. R., Jr. The Anti-Pressor Action of Renal Extracts and Their Capacity to Reduce the Blood Pressure of Hypertensive Rats, *Am J Physiol* **128** 716, 1940. Williams, J. R., Jr., Grollman, A., and Harrison, T. R. The Reduction of the Blood Pressure of Hypertensive Dogs by the Administration of Renal Extract, *ibid* **130** 496, 1940. Grollman, A., Williams, J. R., Jr., and Harrison, T. R. Reduction of Elevated Blood Pressure by Administration of Renal Extracts, *J A M A* **115** 1169 (Oct 5) 1940.

46 Page, I. H., Helmer, O. M., Kohlstaedt, K. G., Fouts, P. J., Kempf, G. F., and Corcoran, A. C. Substance in Kidneys and Muscle Eliciting Prolonged Reduction of Blood Pressure in Human and Experimental Hypertension, *Proc Soc Exper Biol & Med* **43** 722, 1940.

in pressure remains for several days, in contradistinction to the transient reduction resulting from injection of histamine, choline, adenylic acid, etc

Various drugs and extracts⁴⁷ have been tested in regard to their effect on the blood pressure of rats and dogs with renal hypertension. None save renal extracts had an appreciable effect in lowering the blood pressure, and the clinical value of so-called depressor substances is thus questionable. The administration of relatively large doses of sodium chloride did not markedly elevate the blood pressure.

Essential Hypertension—Last year we reviewed⁴⁸ in detail an article by Robinson and Bruce⁴⁹ on the range of normal blood pressure. The validity of any conclusion which was based on their statistical method has been called into question by Treloar.⁵⁰ The conclusions presented by Robinson and Bruce are of such importance that an effort should be made to lift them above all possible criticism or to alter them if found incorrect.

Robinson and his associates have continued their interesting studies on blood pressure. Hypotension⁵¹ (blood pressure below 110 systolic and 70 diastolic) is regarded not as a disease but as an ideal blood pressure level. In regard to body build,⁵² it was found that persons of linear (narrow-chested) build had lower blood pressures than persons of lateral (broad-chested) build and that hypertension tended to develop less frequently in the former. Because of this positive correlation the authors regard the hereditary predisposition to normal pressure and to hypertension as an established fact. In regard to obesity,⁵³ it was found that there was a steplike rise in blood pressures with an increase in ponderal index (weight divided by height) toward obesity. It is pointed out that the significance of this fact must be withheld until the influence of body build on obesity has been appraised.

47 Grollman, A., Harrison, T. R., and Williams, J. R., Jr. Therapeutics of Experimental Hypertension, *J Pharmacol & Exper Therap* **69** 76, 1940. Wakerlin, G. E., and Games, W. The Effect of Various Agents on the Blood Pressure of Renal Hypertensive Dogs, *Am J Physiol* **130** 568, 1940.

48 Graybiel, A., and White, P. D. Diseases of the Heart. A Review of Significant Contributions Made During 1939, *Arch Int Med* **65** 1053 (May) 1940.

49 Robinson, S. C., and Bruce, M. Range of Normal Blood Pressure. A Statistical and Clinical Study of 11,383 Persons, *Arch Int Med* **64** 409 (Sept) 1939.

50 Treloar, A. E. Normal Blood Pressure, *Arch Int Med* **66** 848 (Oct) 1940.

51 Robinson, S. C. Hypotension. The Ideal Normal Blood Pressure, *New England J Med* **223** 407, 1940. Treloar⁵⁰

52 Robinson, S. C., and Bruce, M. Body Build and Hypertension, *Arch Int Med* **66** 393 (Aug) 1940.

53 Robinson, S. C., Bruce, M., and Mass, J. Hypertension and Obesity. Statistical and Clinical Study of 10,883 Individuals, *J Lab & Clin Med* **25** 807, 1940.

The surgical treatment of hypertension by means of bilateral splanchnicectomy continues to be favorably reported on⁵⁴ De Takats and Scupham⁵⁵ decapsulated the kidneys and wrapped omentum or a pedicled muscle flap around those organs in 4 cases of hypertension with malignant nephrosclerosis There was no definite improvement in any case

There have been a number of reports⁵⁶ in regard to the association of hypertension and disease of the kidneys The general conclusion is reached that only an occasional patient is benefited by removal of the diseased kidney and that removal should be for reasons other than the relief of hypertension

CORONARY HEART DISEASE

Blumgart, Schlesinger and Davis⁵⁷ have described in great detail a joint clinical and pathologic study of autopsy records of 125 consecutive cases in which clinical manifestations of angina pectoris, coronary thrombosis, myocardial infarction and congestive failure were related to pathologic changes observed in the coronary arteries and in the heart muscle Thirty cases representing all the patients with clinical evidence of car-

54 Peet, M M , Woods, W W , and Braden, S The Surgical Treatment of Hypertension Results in Three Hundred and Fifty Consecutive Cases Treated by Bilateral Supradiaphragmatic Splanchnicectomy and Lower Dorsal Ganglionectomy, *J A M A* **115** 1875 (Nov 30) 1940 Allen, E V , and Adson, A W The Treatment of Hypertension Medical Versus Surgical, *Ann Int Med* **14** 288, 1940

55 de Takáts, G , and Scupham, G W Revascularization of the Ischemic Kidney, *Arch Surg* **41** 1394 (Dec) 1940

56 Crabtree, E G , Pyelonephritic Injuries to the Kidney and Their Relation to Hypertension, *J Urol* **44** 125, 1940 Barker, N W , and Walters, W Hypertension and Chronic Atrophic Pyelonephritis Results of Nephrectomy, *J A M A* **115** 912 (Sept 14) 1940 Nesbit, R M , and Ratliff, R K Hypertension Associated with Unilateral Renal Disease, *ibid* **116** 194 (Jan 18) 1941 Palmer, R S , Chute, R , Crone, N L , and Castleman, B The Renal Factor in Continued Arterial Hypertension Not Due to Glomerulonephritis as Revealed by Intravenous Pyelography A Study of Two Hundred and Twelve Cases, with a Report of the Results of Nephrectomy in Nine Cases, *New England J Med* **223** 165, 1940 Schroeder, H A , and Fish, G W Studies on "Essential" Hypertension III The Effect of Nephrectomy upon Hypertension Associated with Organic Renal Disease, *Am J M Sc* **199** 601, 1940 Braasch, W F , and Jacobson, C E Chronic Bilateral Pyelonephritis, *J Urol* **44** 571, 1940 Braasch, W F , Walters, W , and Hammer, H J Hypertension and the Surgical Kidney, *J A M A* **115** 1838 (Nov 30) 1940 Crabtree, E G , and Chaset, N Vascular Nephritis and Hypertension A Combined Clinical and Clinicopathologic Study of One Hundred and Fifty Nephrectomized Patients, *ibid* **115** 1842 (Nov 30) 1940

57 Blumgart, H L , Schlesinger, M J , and Davis, D Studies on the Relation of the Clinical Manifestations of Angina Pectoris, Coronary Thrombosis, and Myocardial Infarction to the Pathologic Findings, with Particular Reference to the Significance of the Collateral Circulation, *Am Heart J* **19** 1, 1940

diac pain or congestive failure or with anatomic evidence of coronary occlusions were compared with the remaining 95 cases. The authors' chief conclusions, in part, are as follows:

In normal hearts, intercoronary anastomoses larger than 40 micra in diameter are not found.

Obstruction to normal coronary arterial blood flow by arteriosclerotic narrowing or occlusion regularly results in the development of intercoronary anastomoses measuring 40 to 200 micra in diameter.

Such anastomotic circulation may so well compensate for occlusion or marked narrowing of a major coronary artery that the blood supply to the heart remains adequate for the ordinary activities of life. When the narrowing or occlusion progresses so far that the coronary circulation is insufficient to meet the needs of the heart during periods of increased work, myocardial anoxemia results. The "coronary reserve" is clearly reduced. The frequency of angina pectoris in patients who show such pathologic changes is in accord with these considerations.

The pathologic basis for congestive failure in patients with coronary arterial disease or angina pectoris was studied. The results suggest that constantly undernourished areas in hearts which are the seat of coronary arteriosclerosis, when subjected to still greater anoxemia, such as is brought about by exertion or emotion, undergo focal necrosis and a diffuse fibrous change. The replacement by connective tissue leads to myocardial weakness and congestive failure. The hearts with the greatest amount of replacement of myocardial fibers by fibrous tissue were found in patients who, after some months or years of angina pectoris, finally developed congestive failure.

A comparative study of the clinical characteristics of coronary thrombosis and those of myocardial infarction forces the conclusion that coronary thrombosis and occlusion, per se, do not necessarily produce any characteristic clinical manifestations. If an occlusion occurs gradually, over months or years, with the concomitant development of an anastomotic circulation, no symptoms or signs will be produced and no myocardial lesions will be demonstrable.

The syndrome usually called "coronary occlusion," which consists of prolonged substernal oppression or pain, a fall in blood pressure, pallor, and other manifestations of shock, and is accompanied by electrocardiographic changes, fever, leucocytosis, and an increased sedimentation rate, in reality signifies myocardial infarction, and should be so termed.

Attacks of severe, prolonged pain, associated at times with collapse, evidently result from prolonged insufficiency of the blood supply to the myocardium and consequent anoxia. This "coronary failure" may occur with or without simultaneous, or immediately preceding, coronary thrombosis.

If such "coronary failure" is sufficiently prolonged, myocardial infarction results. This may be obviated in some instances, however, if the demands on the myocardium are quickly reduced by rest in bed, sedatives, or the control of rapid ventricular rates.

In the hearts of several patients in which the coronary blood flow was already reduced and presumably slowed because of occlusions and narrowing, the sudden fall in blood pressure which accompanied postoperative shock evidently led to further stagnation, anoxemia, and the deposition of multiple coronary thrombi. The importance of avoiding a fall in blood pressure, whatever the cause, in cases of coronary arteriosclerosis is emphasized.

Απολία, necrosis, infarction, and fibrosis of the myocardium, and their accompanying clinical manifestations, arise whenever there is a discrepancy between the nutritional requirements of the heart muscle, on the one hand, and the factors governing nutritional supply, on the other. The extraordinary significance of the collateral circulation in bridging the discrepancy between supply and demand is emphasized.

Fauteux⁵⁸ has described a new surgical procedure for the treatment of coronary arteriosclerosis. He points out that one of the fundamental principles in surgical treatment of peripheral vascular disorders is the desirability of ligating the companion vein whenever a major artery is ligated or diseased. The beneficial effect of this procedure is brought about by maintaining within the limb for a longer period the smaller amount of blood supplied by the collateral circulation. Fauteux applied this method in experiments on the dog's heart. He found that whereas resection of a portion of the ramus descendens of the left coronary artery was almost always fatal, if the companion vein was ligated at the same time the dogs survived. Even when the arterial resection was carried out months after the ligation of the vein the animals survived. These results suggested that "in cases properly selected coronary vein ligation may be expected to act as a preventive measure against a second attack of coronary thrombosis and also to improve the coronary circulation sufficiently to relieve the pain of 'angina of effort'."

Raab⁵⁹ has reported his results on the treatment of 100 patients with angina pectoris by means of roentgen irradiation of the adrenal glands. Symptoms were relieved in 76 of the 100. Of the 76, 62 "were entirely or almost entirely freed from complaints or, at least, considerably improved" for an average period of thirteen and one-half months, and the remaining 14 were moderately improved during an average period of seven and a half months. We are frankly skeptical of these results, having used a similar procedure in a small number of cases without success.

TREATMENT OF HEART FAILURE

Although galenic preparations of digitalis have enjoyed widespread preference among physicians in this country, intense interest has been maintained in the purified glucosides of this drug. It has long been the ambition of some investigators to isolate all the glucosides of digitalis, explore the therapeutic possibilities of each separately and then synthetically regroup them in order to reconstruct the global effect of the drug. Recent studies have emphasized the importance and therapeutic

58 Fauteux, M. Experimental Study of the Surgical Treatment of Coronary Disease, *Surg, Gynec & Obst* **71** 151, 1940.

59 Raab, W. Roentgen Treatment of the Adrenal Glands in Angina Pectoris (One Hundred Cases), *Ann Int Med* **14** 688, 1940.

value of lanatosid C ($C_{49}H_{76}O_{20}$) ⁶⁰ Kwit, Gold and Cattell ^{60b} have observed that lanatosid C compared favorably with digitalis leaf in a study of a selected group of 67 patients, some with auricular fibrillation and others with regular sinus rhythm Fahr and La Due ^{60c} found this glucoside to be as effective therapeutically in cases of heart failure with normal rhythm as in cases of auricular fibrillation Kwit and associates observed that the range between the therapeutic dose and the toxic dose for lanatosid C in man is similar to that for the digitalis leaf but that the former is not rapidly absorbed, since it requires many times the intravenous dose to cause similar effects by oral administration The full digitalizing dose of lanatosid C by intravenous injection is about 1.5 mg (6 cat units) given within two to three hours The desirability of such a preparation which may not require bioassay is readily apparent

MISCELLANEOUS

Kinked Carotid Artery—Parkinson, Bedford and Almond ⁶¹ have described the so-called kinked carotid artery on the basis of 47 of their own cases and a review of those previously published The common form of kinked carotid artery is generally associated with hypertension or with arteriosclerosis or with the two in combination and occurs in elderly women, especially those with spinal curvature and obesity, it is scarcely ever seen in men The swelling consists of an arterial prominence in the region of the bifurcation of the innominate artery and may be formed by a loop of the right carotid artery, though the innominate and the subclavian artery may contribute There are no symptoms beyond local throbbing, and prognosis is not adversely affected

Gonorrheal Myocarditis—Bang ⁶² has attempted to show that gonorrheal myocarditis may be a fairly frequent complication of gonococcal infection, having observed 6 cases in the course of one year in a medical ward The diagnosis was made chiefly on the basis of electrocardiographic changes developing during the course of complicated gonorrhea He further suggests that while in some cases the myocarditis is slight and transitory, in others it may lead to chronic degenerative heart disease

60 (a) Kaplan, J. J., and Visscher, M. B. Comparative Toxicity Studies of the Glucosides of Digitalis Lanata in the Pigeon, Cat and Dog, with Some Observations on the Influence of Anesthesia, *J. Pharmacol. & Exper. Therap.* **70** 228, 1940 (b) Kwit, N. T., Gold, H., and Cattell, M. Studies on Purified Digitalis Glucosides. II. Potency and Dosage of Lanatoside C in Man, *ibid.* **70** 254, 1940 (c) Fahr, G. E., and La Due, J. S. Personal communication to J. J. Kaplan and M. B. Visscher, 1940

61 Parkinson, J., Bedford, D. E., and Almond, S. The Kinked Carotid Artery That Simulates Aneurysm, *Brit. Heart J.* **1** 345, 1939

62 Bang, O. Gonorrheal Myocarditis, *Brit. M. J.* **1** 117, 1940

We are of the opinion that the latter conclusion is not established by the available data and is, moreover, unlikely to prove true

Pulmonary Embolism—Pulmonary embolism is of particular interest to cardiologists because it may simulate or complicate heart disease. Recent studies⁶³ have added to knowledge of this disorder. White points out^{63d} that pulmonary embolism frequently goes unrecognized and that its detection will often explain obscure signs and symptoms, refractoriness to treatment and periodic episodes of fever, tachycardia or collapse. That consideration be given to the following clues to the diagnosis of obscure pulmonary embolism is recommended by White and other authors: (1) the occurrence of unexplained fever, leukocytosis, tachycardia, faintness, prostration, dyspnea, asthma or even jaundice (from hemolysis of a large infarct plus an engorged liver), especially in a patient with heart disease (particularly in the presence of mitral stenosis or heart failure), (2) the finding of pulmonary signs (rales or consolidation) not adequately explained by either congestive heart failure or pulmonary infection, (3) the periodic recurrence at short intervals of episodes that individually might be mistaken for acute coronary occlusion but which in series are much more likely to mean repeated pulmonary embolism, (4) the inexplicable lack of response in a case of congestive heart failure to therapy which seemingly should be adequate (other factors, such as infection, infarction elsewhere than in the lungs and thyrotoxicosis being ruled out), and (5) in a few cases, the occurrence of the electrocardiogram characteristic of acute cor pulmonale (prominent S waves in lead I, low, flat or even inverted T waves in lead II, prominent Q waves and inverted T waves in lead III, and low, flat or inverted T waves in lead IV) when the right ventricle is dilated by a massive embolism (not, therefore, in the majority of cases of pulmonary embolism) and simulating at first glance the electrocardiogram of acute coronary thrombosis with basal infarction.

63 (a) Parsons-Smith, B. Pulmonary Embolism and Infarction, *Brit M J* **2** 179, 1940. (b) Stewart, H. J., Kirk, R. C., and Smith, J. J. Electrocardiographic Changes in Pulmonary Infarction, *Internat Clin* **3** 135, 1940. (c) Sokolow, M., Katz, L. N., and Muscovitz, A. N. The Electrocardiogram in Pulmonary Embolism, *Am Heart J* **19** 166, 1940. (d) White, P. D. Pulmonary Embolism and Heart Disease. A Review of Twenty Years of Personal Experience. *Am J M Sc* **200** 577, 1940.

News and Comment

Directory of Medical Specialists—A second edition of the Directory of Medical Specialists has been authorized by the Advisory Board for Medical Specialties, to be ready for distribution in February 1942, with its contents complete to January 1. This directory, the official publication of the Advisory Board, will list the names of approximately 18,000 diplomates of the fifteen American boards examining candidates for certification in the specialties. This number is an increase of 4,000 over those listed in the first edition, issued early in 1940. The geographic grouping will give completely revised biographic data about each diplomate, there will be an alphabetic index, with addresses and specialty designations, and a full outline of the plan of organization, the officers and the examination requirements of each American board.

Information not found in the first edition will be included in the second, such as details of formal training and military appointments.

All who have been formally certified by one of the American boards will be included.

The publication is issued through the Columbia University Press, New York. The secretary of each specialty board serves on the Advisory Editorial Board, and Dr. Paul Titus, 1015 Highland Building, Pittsburgh, of the American Board of Obstetrics and Gynecology, is the directing editor.

1941 Graduate Fortnight of the New York Academy of Medicine—The New York Academy of Medicine will hold a Graduate Fortnight Oct. 13-24, 1941. The subject for discussion will be "Cardiovascular Diseases, Including Hypertension."

Members of the medical profession are eligible for registration.

A complete program and registration blank may be secured by addressing Dr. Mahlon Ashford, 2 East One Hundred and Third Street, New York.

Book Reviews

Applied Pharmacology By Hugh Alister McGuigan, Ph D, M D, F A C P, Professor of Pharmacology and Therapeutics, University of Illinois College of Medicine Price, \$9 Pp 914 St Louis C V Mosby Company, 1940

The title of this book is misleading It is not in any sense a manual of therapeutics, nor is it a discussion of the modification of physiologic processes such as that given in the text by Clark, published under this same title since 1923 While there is no reference in the preface to the author's earlier text "Pharmacology and Therapeutics" (1928), the two follow the same general plan, and at least part of the newer volume has been taken bodily from the older

The factual material of pharmacology has come to be so extensive that the chief problem of those who are responsible for presenting it either in classroom or text is one of selection There is compiled a tremendous amount of information in the volume under consideration Each drug is discussed after the conventional pattern, i e, members of its group, chemistry, pharmacodynamics, toxicology, therapeutic uses, preparations, etc A considerable amount of review of physiologic mechanisms is scattered throughout the text, sometimes in relation to the context However, the reviewer feels that the book lacks a broad plan and that there is therefore considerable disorganization Although there are no divisions into numbered chapters with appropriate titles, both the table of contents and the size of type and placing of headings indicate, or should indicate, the subdivision of material Actually, this subdivision often follows no recognizable pattern For example, functions of the stomach, hypersecretion and peptic ulcer are discussed under "Deglutition" Thiocyanates are considered under "The Reticuloendothelial System" Perhaps worst of all, not only are radium, lead, iron and aluminum listed under "The Chemotherapy of Syphilis," but the running title for each page of discussion of these subjects is also "Chemotherapy of Syphilis"

In a book of this length a reviewer must be content with samples taken at random Such samples reveal some serious errors of fact The solution of posterior pituitary U S P is said to be standardized by comparison with histamine It is true that the assay introduced into the Pharmacopeia of the United States IX was based on this comparison, but this method has not been official since Jan 1, 1926 It is always an error to refer to a commercial preparation with a distinctive trade name as an internal secretion "At least two internal secretions (pitressin and cortin) have a definite effect on the secretion of the urine" (page 389) According to the author's own statement (page 853), pitressin "is an aqueous preparation of the posterior lobe containing 20 units of the pressor principle per cubic centimeter Five-tenths per cent chlorbutanol is used as a preservative" The author is not the only one to fall into this error

Although many structural formulas are given, it is rather surprising to find that for morphine omitted, especially in view of the large amount of work done during the last ten years on the effect of modification of this substance The section on the action of the opium group on the gastrointestinal tract is apparently taken verbatim from the 1928 text, and no references are made to the extensive recent work in this field The amount of discussion of different groups of drugs does not always seem well balanced For example, barbiturates are given five pages and the sulfone group of hypnotics half as many Benzene and other cyclic hydrocarbons are discussed between the introductory section on the nervous system and that on alcohol Both the U S P and the B P preparations are listed without critical evaluation, but indication is not given as to the particular revision of either the Pharmacopeia of the United States or the British Pharmacopoeia intended

It seems to the reviewer that a large manual of this sort, one that is probably too large for a textbook, ought to be as free as is humanly possible from errors of fact or implication, and its organization should be such as to make possible its use for reference with a minimum amount of effort. It is not enough that there be evidence of much labor. There is such evidence here, and there is here compiled a great deal of valuable material not always easy of access. But the apparent lack of a broad plan of organization and of an exacting editorial supervision has to a large degree nullified the efforts of the author. The book cannot be commended.

Treatment of Diabetes Mellitus By Elliott P. Joslin, M.D., Sc.D., Howard F. Root, M.D., Priscilla White, M.D., and Alexander Marble, M.D. Price, \$7.50. Pp. 783. Philadelphia: Lea & Febiger, 1940.

It is remarkable that so much new material can be incorporated in a revision of a book on a subject, diabetes, on which in the minds of many people information has been more or less static since the developments following the discovery of insulin. Joslin's standard book on diabetes in its present seventh edition has 756 pages of text, as compared with the sixth edition with 686 pages, which was published in 1937. There are new statistics, new facts and even new cooperating authors. The different chapters are revised and rewritten not only by the three, Root, White and Marble, who cooperated with Joslin in the sixth edition, but by others who appear as co-authors of chapters, including McDaniel, Pincus and Baldwin. Outstanding in the new material is the recognition by Joslin of the work of Best and Lukens on the relation of the anterior lobe of the pituitary gland to diabetes and to the pancreas itself. In his preface, Dr. Joslin says that it gives him a thrill to read that "diabetes resulting from the injection of anterior pituitary extract actually can be prevented," and to be told and shown that it can be cured, if as yet only in a dog or a cat. If prevention and cure are possible in an animal, why not in man?

The authors advocate treating the patient with diabetes so that the blood sugar is maintained at approximately normal figures while the patient is kept aglycosuric. This method is in contradistinction to that of some workers on diabetes who maintain that maintenance and physical well-being constitute the ultimate criterion for proper treatment of the diabetic patient.

It would be redundant to recount the contents of a book which has gone through seven editions, which is looked on as the bible of all who treat diabetic patients and which has had fulsome praise from every reviewer of previous editions. Suffice it to say that "Treatment of Diabetes Mellitus" by Joslin is a medical classic.

Rheumatic Fever By May G. Wilson, M.D. Price, \$4.50. Pp. 595. New York: The Commonwealth Fund, 1940.

This book, a summary of the author's experience in the observation of rheumatic fever in the first three decades of life, is based on first hand information obtained from the study of 647 subjects selected from 1,000 patients.

The first chapter contains a short but interesting historical summary of rheumatic fever. In the second chapter the epidemiologic aspects of the disease are dealt with and effects of climate, season, economic status, contagion and heredity are considered. The author concurs in the opinion of the English commission that overcrowding and poverty are not prime factors in the determination of the incidence of rheumatic fever and states that there is no conclusive evidence of contagion in the production of the disease, "although many of the facts are consistent with this view." The most arresting observation relating to the epidemiologic aspects is that heredity plays an extremely significant role in the production of rheumatic fever. For example, it was found that if both parents have a history of rheumatic fever, it may be predicted that the disease will affect practically all the progeny. If one parent has such a history and if one grandparent on the opposite side has a history of the disease, 50 per cent of the progeny will have rheumatic

fever If this point of view is confirmed by other careful studies it will be of tremendous importance in any program in which reduction of the incidence of the disease is sought

The fourth chapter concerns etiologic factors Evidence for and against theories for the bacterial, allergic and virus origin of the disease is considered, and the conclusion is reached that there are serious objections to acceptance of any of the aforementioned factors as the proved cause of rheumatic fever In this connection the author records her failure to produce rheumatic fever in chimpanzees inoculated with material obtained from patients with rheumatic fever She refers to her experience that the incidence of positive blood cultures and the type of organism recovered were about the same among subjects recovering from acute infections as among patients suffering from rheumatic fever, and she concludes that infection of the respiratory tract is not a specific provocative agent in the occurrence of rheumatic fever

Valuable chapters on pathologic changes, prognosis, criteria of diagnosis, significance of physical signs, roentgenographic and electrocardiographic studies and general and "specific" therapeutic measures follow The inclusion of extensive and detailed records of the patients observed permits study of the material at first hand

This record of a prodigious amount of personal observation and critical evaluation of a wealth of material should become required reading for the student of rheumatic fever

Electrocardiography By Chauncey C Maher and Paul H Wosika Third edition, revised Price, \$4 Pp 334, with 147 illustrations Baltimore The Williams & Wilkins Company, 1940

The third, revised edition of Maher's book is a distinct improvement over the preceding ones The detailed criticism of the second edition (*J A M A* 109 1223 [Oct 9] 1937) has borne fruit in a thorough correction of some errors in the text, particularly in the presentation of the electrocardiograms In the present edition, the electrocardiograms and their descriptions are on facing pages, an arrangement which simplifies the study of them and eliminates the interruptions in the text An excellent correlation is achieved by presenting at the start of the book the classification of the Criteria Committee of the New York Heart Association and by rigidly adhering to its nomenclature throughout The arrhythmias are well presented, as they should be The chapter "The Electrocardiogram in Coronary Disease" is well done and should give the general reader a modern conception of this controversial subject The electrocardiograms that illustrate this section are less striking than they might have been In the cases of coronary occlusion, where serial electrocardiograms are reproduced, the time interval between tracings is excessively long, viz one, seven and seventy days, six hours and twenty-five days, twenty-four hours, two days and ninety days, one and four days Furthermore, while the author points out that a later tracing is often necessary to corroborate a diagnosis of coronary occlusion, he does not make it quite clear that these later tracings follow a pattern of repair of the injury The greatest usefulness of such tracings, then, is the evidence they supply of a normal (or uncomplicated) recovery from the accident Chapter XIII, "Clinical Syndromes and Electrocardiographic Diagnosis," will appeal to the general reader who expects the electrocardiogram to clarify his clinical suspicions The broad generalities in this section are probably correct, and the emphasis is properly placed on the electrocardiogram as but one of the diagnostic tools, rather than as *the* diagnostic tool, for cardiac disease

The book would be considerably improved by three changes 1 The use, as again suggested, of reproductions of the electrocardiograms rather than of retracings, which are often difficult to read 2 A separate index of the electrocardiograms that illustrate the text, so that the busy student or practitioner can find sample tracings readily The text would be easier to follow if when an electrocardiogram is referred to, the page on which it is reproduced is mentioned 3

More careful editing by the publishers. However, the book will be valuable to the students and the general practitioners who are seeking practical knowledge of electrocardiography presented in a manner that can be understood.

Strange Malady The Story of Allergy By Warren T. Vaughn, M.D., with a foreword by Esmond R. Long, M.D. Price, \$3. Pp. 268. New York: Doubleday, Doran & Company, Inc., 1941.

Sponsored by the American Association for the Advancement of Science, this new book is the second of a series of nontechnical volumes on scientific subjects.

Allergy is a popular medical subject, and in this volume the general reader is told the story of allergy in a clear, readable style by an outstanding authority.

Many physicians will also appreciate and enjoy this review, and for senior medical students, interns or those intending to embark on the practice of allergy, the book will be an excellent introduction to the general subject.

The first portion of the book, devoted to the history and background of present day allergy, is particularly fascinating. Several of the men who contributed most to the subject of the relationship of immunology and allergy, such as Ehrlich, Sewall, von Behring and Calmette, were contemporaries and friends of the author's father, Dr. Victor Vaughn, himself a pioneer in the field. Hence the author is able to draw on memories and anecdotes of these great men, thereby adding much to the interest and value of this portion of the book. Ehrlich's side chain theory of the processes of immunity and allergy is clearly presented, but to make the material entirely unmistakable excellent line drawings and cartoons illustrating the theory accompany the text.

The second portion describes allergic diseases, their numerous causes, how the causative agent is found and how allergic diseases are treated. The layman will enjoy this portion as he would a series of short detective stories.

The internist or neurologist will probably not agree with the statement that migraine headache is one of the "commoner allergic diseases." The consulting allergist, however, doubtless sees a higher incidence of allergic headache than does the physician in general practice. The internist also may question the opinion that "sensitization to foods is the commonest form of human allergy" and may not have the confidence in cutaneous tests with food antigens that may be inferred from the chapter on "Forbidden Fruit."

The closing chapters deal somewhat with problems for the future and the part that nervous factors, internal secretions, histamine and so forth may play in the development of allergic conditions.

Bacteriology in Neuropsychiatry By Nicholas Kopeloff, Ph.D. Price, \$4.50. Pp. 316. Springfield, Ill.: Charles C. Thomas, Publisher, 1941.

This is a readable survey of an enormous amount of literature on the infectious diseases which may be related to pathologic conditions of the human nervous system. The book is particularly valuable as an aid to the investigator. Although it is by no means a complete textbook on bacteriology, it has covered many fields not dealt with in texts, particularly the investigation on the bacteriology of the so-called functional nervous diseases. There are eight chapters on the possible relationship of infection to the functional psychosis and to epilepsy. Combining the literature and offering the results of his own work in this field, the author discounts focal infection, autointoxication and "filterable forms of tuberculosis" as being of primary importance in such conditions; also, he finds that the body fluids of psychotic patients do not differ substantially from those of normal persons. There are four interesting chapters on allergy and hypersensitiveness.

The following items were of interest. The epidemiologic studies on the encephalitis occurring in St. Louis suggest the possibility of rodents being a vector in the spread of the disease. Anterior poliomyelitis virus is present in the gastrointestinal tract of patients, and there is considerable evidence for the spread of the virus via sewage. In regard to smallpox, it is interesting that the number of

cases of postvaccinal encephalitis is declining. Mumps may spread through army camps, and the disease shows a high incidence of associated mild meningoencephalitis. Influenza virus exists as a saprophyte in the larva of the swine lung worm, as has been shown by Francis. Attention is called to Stanley's statement that the basic unit of the filtrable virus is a "gene, perhaps a single nucleoprotein molecule."

Possibly the greatest value of the book is the clarifying of the significance both of a large amount of confusing literature and of a number of bacteriologic studies of questionable worth.

Management of the Cardiac Patient By W. G. Leaman Jr., M.D., Assistant Professor of Medicine, Woman's Medical College of Pennsylvania. Price, \$6.50. Pp. XX + 705, with 255 illustrations. Philadelphia: J. B. Lippincott Company, 1940.

Heart disease, no doubt, deserves unending attention. This new textbook is a workman-like affair, clearly printed, delightfully illustrated, well indexed and not too heavy for comfortable use in spite of its length. When the second edition appears, a better picture of William Withering or an improved reproduction of the title page of the first edition of his "Account of the Foxglove" would make a more dignified frontispiece than the one now used. This, however, is a minor criticism.

The book is built along orthodox lines and reads easily. Certain subjects which often receive scant attention in medical texts are properly emphasized: social service, physical therapy, occupational therapy and prescribed exercise. The surgical and obstetric aspects of heart disease also receive the serious consideration which they deserve.

The book is pleasant to meet.

An Introduction to Biochemistry By W. R. Fearon. Second edition. Price, \$3.75. Pp. 475. St. Louis: C. V. Mosby Company, 1940.

This is a textbook of 475 pages. The approach to the subject is with special emphasis on inorganic biochemistry, with correspondingly less emphasis on organic chemistry, tissue chemistry, blood, muscle and nerve.

This, the second, edition has been largely rewritten. Special chapters are provided for solutions and colloidal systems, steroids, pigments, tissue respiration and internal environment.

References are placed at the end of each chapter.

The difference in emphasis notable among British writers on biochemistry is exemplified in that as much space is devoted to the effect of osmotic salts on the maintenance of fluid equilibrium in elasmobranchs as is given to the essential amino acids (one-third page).

The material is presented in brief, concise form and is adequately systematized.

Synopsis of Materia Medica, Toxicology and Pharmacology By Forrest Ramon Davison. Price \$5. Pp. 633, with 45 illustrations. St. Louis: The C. V. Mosby Co., 1940.

Here indeed is an excellent book of convenient size including the essentials of materia medica, toxicology and pharmacology. Introductory chapters deal with such subjects as basic principles of pharmacology, prescription writing and toxicology, and these are followed by systematic discussions of various groups of drugs. Of special value to the physician are the pages dealing with newer drugs, in regard to which material is hard to find in most textbooks. Diagrams, kymographic tracings and drug formulas enrich the text, which is well printed on substantial paper.

FULMINATING BACILLUS COLI SEPTICEMIA IN WOMEN WITH DIABETES

REPORT OF FOUR CASES, WITH SPECIAL REFERENCE
TO CLINICAL DIAGNOSIS

BYRON D BOWEN, M D

Associate Professor of Medicine, University of Buffalo School of Medicine
AND

ERNEST WITEBSKY, M D

Bacteriologist and Serologist, Buffalo General Hospital, Associate Professor
of Bacteriology and Immunology, University of Buffalo School of Medicine
BUFFALO

In September 1938 an obese woman with diabetes was admitted to the Buffalo General Hospital in a stuporous state, from which she gradually lapsed into unconsciousness. She presented a clinical picture such as we had not seen before. High fever and leukocytosis were present, and the only apparent cause for this was that suggested by the finding of pus and bacteria in the urine. The patient had been acutely ill for only a day. Treatment was directed toward the diabetes, but she lived only three days. No diagnosis was made until the blood culture, which was taken soon after admission, showed a pure growth of *Bacillus coli*.

Within a period of less than a year 3 more patients presented a clinical picture so similar to that of the first patient that the diagnosis was readily suggested, and treatment was instituted before the blood cultures had yielded growth. These 4 cases are presented to call attention to the similarity and dissimilarity between the symptoms of the disease to be described and those of diabetic coma. Further, we wish to stress the importance of an early diagnosis of this apparently fulminating form of *Bacillus coli* septicemia in women with diabetes if chemotherapy is to be attempted.

REPORT OF CASES

CASE 1—Mrs Z, aged 63, was admitted to the Buffalo General Hospital Sept 22, 1938 and died on September 25. She was known to have had diabetes

From the Medical Service of the Buffalo General Hospital

Presented at the Fifty-Seventh Annual Meeting of the American Clinical and Climatological Association, White Sulphur Springs, W Va, Oct 28, 1940

for three years. A diet and insulin were prescribed by her physician, but neither counsel was obeyed. She had been up and around the house until the day before admission, when she suddenly complained of "being cold." She went to bed, and drowsiness soon ensued.

Examination showed a rather stout woman in a state of restless stupor. Her face was flushed, and her rectal temperature was 104 F. Her breathing was rapid and irregular but not of the Kussmaul type. Her pulse was rapid and bounding, the blood pressure was 210 systolic and 110 diastolic. Her lungs were clear except for rales heard at the base of the right lung posteriorly, where there was a slight prolongation of expiration. The abdomen was normal except that the liver was palpable a few centimeters below the costal margin. There was no evidence of meningeal irritation or of paralysis.

The urine was cloudy and had a specific gravity of 1.022. It gave an acid reaction. It contained albumin (3 plus) and sugar (3 plus). When tested with sodium nitroprusside, it gave a 1 plus reaction. There was sediment to a depth of 2 mm in the centrifuge tube after spinning, composed entirely of leukocytes, mostly clumped, and bacteria.

The blood contained 400 mg of dextrose and 37 mg of urea nitrogen per hundred cubic centimeters. The carbon dioxide capacity of the plasma was 50 volumes per cent. The red cells numbered 4,250,000, the hemoglobin value was 80 per cent, and the white blood cell count was 24,000 with 88 per cent polymorphonuclears, of which 12 per cent were young forms. The spinal fluid was clear and under a pressure of 144 mm of water. There was but a trace of protein, and the copper reduction was prompt. The colloidal gold curve and the Wassermann reaction were negative. A catheterized specimen of urine showed many white blood cells and gram-negative rods in the smear. The culture showed *B. coli*. The blood culture taken two days after admission also revealed *B. coli*, but these were not identified until after the patient's death.

Course—On admission the patient was treated with insulin, physiologic solution of sodium chloride parenterally and dextrose as well as fluids given by mouth. The stupor increased so rapidly that within twenty-four hours she could no longer be aroused.

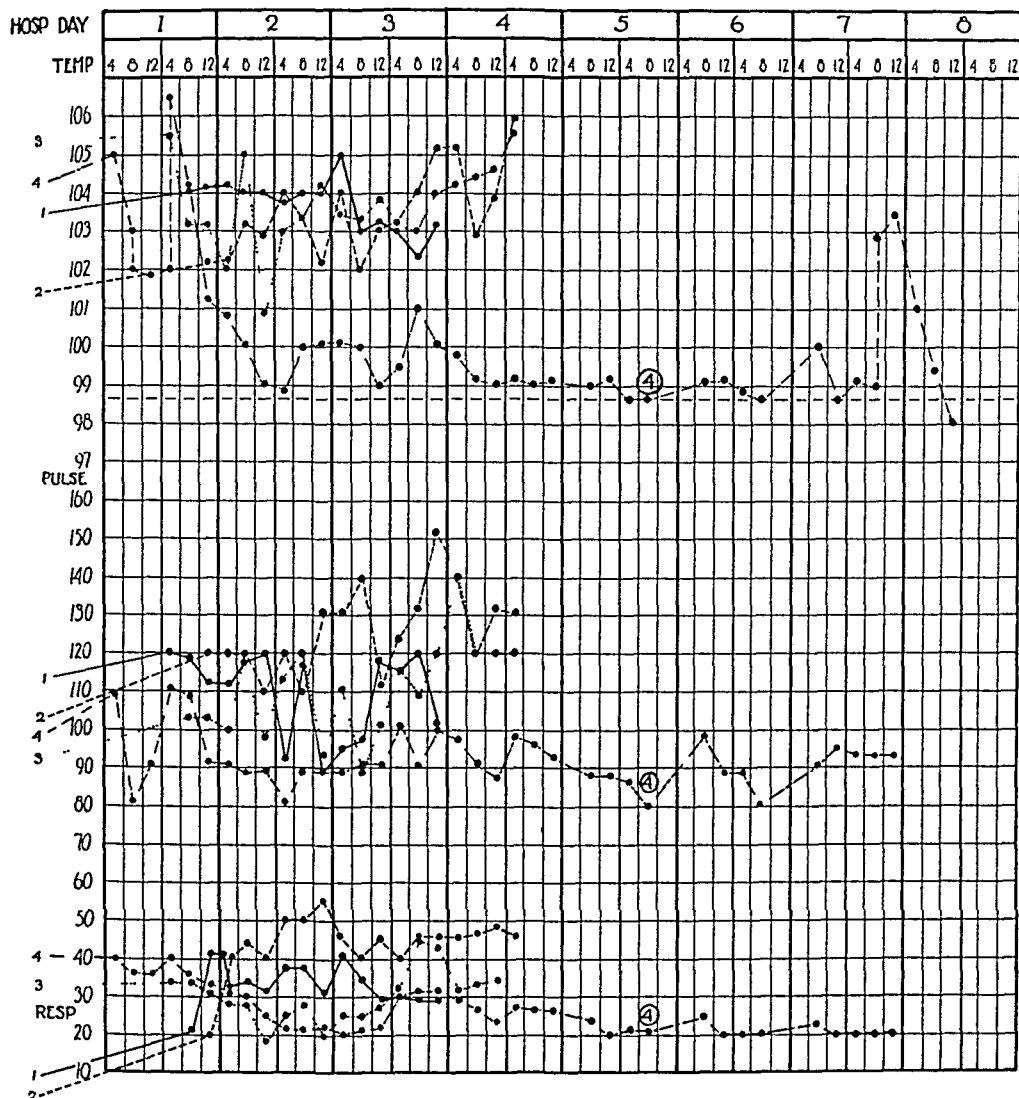
Necropsy (Dr. K. Terplan)—There was marked interstitial pyelonephritis, especially of the left kidney, with multiple bilateral pinhead abscesses, mostly on the under surfaces of the capsules. The smear showed gram-negative rods. Moderate cystitis and ureteritis were present, particularly on the left. The spleen was septic and weighed 500 Gm., the splenic culture showed *B. coli*. There was eccentric hypertrophy of the heart with atherosclerosis of the arch of the aorta and of the coronary arteries. The pancreas weighed 70 Gm. Histologic section of the kidneys showed arteriolar nephrosclerosis with persistence of the embryonal lobulations.

CASE 2—Mrs. G., aged 54, was brought to the Buffalo General Hospital in coma on Nov. 19, 1938 and died three days later. The history was obtained from the family. The patient had been treated in the hospital two years previously and was discharged with prescription of insulin and a diet. She took the insulin for two weeks and was said to have observed the diet for a year. Two days before the second admission nausea and vomiting developed, and she became more and more drowsy.

Examination on admission showed a comatose obese woman. Her rectal temperature was 102.5 F., the pulse rate was 120, the respirations were 40 per minute.

and shallow The blood pressure, taken on two occasions, was 126 systolic and 86 diastolic and 134 systolic and 80 diastolic There were none of the clinical signs of dehydration

The urine was cloudy, and the specific gravity was 1.024 It gave a 3 plus reaction for albumin, and a negative reaction for ferric chloride There was sediment of 5 mm in the bottom of the centrifuge tube, made up almost entirely of white blood cells and motile bacteria The blood dextrose was 888 mg per hundred cubic centimeters The carbon dioxide capacity of the plasma was 60



Composite chart showing temperatures, pulse rates and respiration rates of 4 patients with fulminating *B. coli* septicemia

volumes per cent The spinal fluid was clear, with 6 white blood cells per cubic millimeter, no increase of protein and prompt copper reduction The red blood cells numbered 4,000,000, the hemoglobin value was 82 per cent white blood cells were 18,300 with 75 per cent filamentous and 17 per cent young forms The Wassermann reaction was negative The blood culture which was taken on her second hospital day showed 60 colonies of *B. coli* per cubic centimeter, they, however, were not identified until after the patient's death

Course—At first the patient was treated for diabetic coma with fluids parenterally and large amounts of insulin. There was no change in her condition. The day following admission she was given 500 cc of an 0.8 per cent solution of sulfanilamide subcutaneously. This was repeated the next day. The urea nitrogen content of the blood was not ascertained on the day of admission, but on the second day in the hospital it was 90 mg per hundred cubic centimeters. On the day of her death it was 102 mg. The sulfanilamide in the blood reached a level of 19 mg the day before her death. At that time the carbon dioxide capacity of the plasma was found to have dropped to 38 volumes per cent, possibly as a result of the administration of sulfanilamide. There was no autopsy.

CASE 3—Mrs. W., aged 69, was admitted to the Buffalo General Hospital on July 1, 1939 and died July 4. She was seen by one of us (B. D. B.) in consultation with Dr. Philip Goldstein. It was known that she had had diabetes since 1920. Left hemiplegia occurred in October 1937, from this she recovered. During May 1939 a pain developed in the region of the left hip. About June 1 she had an attack of frequency, urgency and burning of urination, her urine at that time was cloudy. She was treated with sulfanilamide and improved. Before admission to the hospital she had been receiving 20 units of insulin daily. On June 29 a chill developed, her temperature rose to 104 F., and restlessness ensued.

Examination at the hospital showed an obese woman in a state of restlessness and mental confusion. She frequently dozed for short intervals, even during conversation. Her rectal temperature was 105.6 F. Her respirations were rapid and rather deep. There was no clinical evidence of dehydration. A few coarse rales were heard in the right scapular region. The blood pressure was 136 systolic and 78 diastolic. The pulse rate was 112. No explanation was found for the fever on physical examination.

The urine was cloudy, its specific gravity was 1.021. It had an acid reaction. It contained albumin (3 plus) and sugar (3 plus). It gave a 1 plus reaction to the sodium nitroprusside and a negative reaction to the ferric chloride test. The sediment, 0.5 mm in a 15 cc centrifuge tube after spinning, was entirely leukocytes and bacteria. The direct smear of the catheterized specimen showed many leukocytes and gram-positive cocci in chains and a few gram-negative rods. The culture was *B. coli* and enterococci. The blood sugar was 460 mg, urea nitrogen 20 mg, per hundred cubic centimeters. The carbon dioxide capacity of the plasma was 47 volumes per cent. The red blood cells numbered 3,800,000 per cubic millimeter, the hemoglobin value was 80 per cent. The white blood cells numbered 14,800 with 95 per cent polymorphonuclears, 25 per cent of which were band forms. The blood culture taken on admission showed 8 colonies per cubic centimeter. These were not identified until just before the patient's death, another culture taken after she had sulfanilamide showed 10 colonies of *B. coli* per cubic centimeter.

Course—During the first twenty-four hours she was able to take a small amount of food and fluids by mouth. She received only 26 units of insulin during the first twenty-four hours, during this period 4 Gm of sulfanilamide and 25 of sodium bicarbonate were also given. The following day she was considerably worse and would not take anything by mouth. During the next two days she received physiologic solution of sodium chloride and 5 per cent dextrose intravenously and 40 to 50 units of insulin with each 1,000 cc. On July 3 and 4 she

received a total of 160 cc of azosulfamide¹ intramuscularly in doses of 20 cc. She did not become absolutely comatose until twenty-four hours before death. There was no autopsy.

CASE 4—Mrs. B., aged 63, was admitted to the Buffalo General Hospital on July 25, 1939 and discharged on Aug. 6, 1939. She was seen in consultation with Dr. Robert Ullman by one of us (B. D. B.). She had symptoms of diabetes for only a year, during which time her weight decreased from 220 to 205 pounds (99.8 to 93 Kg.). The diabetes had not been treated. The patient dated her acute illness from July 7, 1939, when she noted drowsiness, easy fatigability and frequency and burning of urination. There had also been some loss of appetite and nausea. Her doctor, called just prior to her admission, observed fever.

At the hospital, examination showed an obese woman. Her rectal temperature was 104 F. There was no clinical evidence of dehydration. The patient answered questions readily, but it was difficult to obtain data from her because she had a tendency to drop off to sleep as soon as conversation ceased. The respirations were rapid and deep and were described by the house officer as being of the Kussmaul type. The heart was slightly enlarged, and there was a soft systolic murmur at the apex, which was transmitted over the entire precordium. The blood pressure was 186 systolic and 80 diastolic. There was no evidence of disturbance of the central nervous system.

The urine showed a trace of albumin, contained sugar (4 plus) and gave a 1 plus sodium nitroprusside reaction. The sediment, 2 mm. in a 15 cc. centrifuge tube after spinning, was composed of leukocytes and bacteria. The red cells numbered 4,200,000 per cubic millimeter, and the hemoglobin value was 83 per cent. The white blood cells numbered 14,400, 78 per cent of these were polymorphonuclears, 38 per cent, young forms, 2 per cent, eosinophils, 16 per cent, lymphocytes, and 4 per cent, monocytes. The blood sugar on admission was 512 mg., urea nitrogen, 14 mg., per hundred cubic centimeters. The carbon dioxide capacity of the plasma was 55 volumes per cent. The culture of the urine showed *B. coli*, *Bacillus aerogenes capsulatus* and enterococci. The blood culture showed *B. aerogenes capsulatus*, 50 colonies per cubic centimeter.

Course—The patient was not able to be dieted but took a limited amount of fruit juices by mouth. These were supplanted, however, with physiologic solution of sodium chloride and 5 per cent dextrose solution intravenously, with 30 to 40 units of insulin preceding each clysis of 1,000 cc. She was treated with sulfanilamide twelve hours after admission, she received 3 Gm. during the first twenty-four hours. On the second day she had a chill, and her rectal temperature rose to 106.5 F. Then dosage of sulfapyridine, 1 Gm. every four hours, was started and continued throughout her illness, during the next twelve days she received 60 Gm. by mouth. Her rectal temperature on the next two days rose only to 100 and 101 F., respectively, following the chills.

After her temperature had been normal for three days, she was again catheterized. This was followed by a sharp chill, the temperature rose to 104 F., but immediately receded and did not rise again.

The specimen of urine taken on July 29 still showed many leukocytes and contained *B. aerogenes capsulatus* and enterococci. The white blood cell count con-

¹ Azosulfamide is disodium 4-sulfamidophenyl-2'-azo-7'-acetyl-amino-1'-hydroxy-naphthalene-3',6'-disulfonate. This substance has been known as prontosil soluble, as prontosil and as neoprontosil.

tinued to be high and on August 5 was 18,000 with a considerable shift to the left. The blood culture became negative. When the patient was discharged, however, the urine still contained gram-negative rods and gram-positive cocci, which on culture proved to be *B. aerogenes capsulatus* and enterococci. The diabetes was controlled with a diet of 100 Gm of carbohydrate, 80 Gm of protein and 100 Gm of fat with 50 units of regular insulin daily.

One year after discharge she was receiving 34 units of insulin, and the diabetes was well controlled. The urine was free from pus and bacteria, and the leukocytosis had disappeared.

COMMENT

Septicemia caused by *B. coli*, according to Davis and Turner,² has been reported in the literature in 110 instances in the past fifty years. Presumably many such cases go undiagnosed because of failure to make blood cultures or to make them at the time when bacteremia is present. The mortality rate as observed by a number of authors varies from 30 to 40 per cent, depending somewhat on the source of the infection. Textbook descriptions of septicemia due to *B. coli* indicate that there is no characteristic clinical picture. This may be said of most septicemias. It is well known that fulminating septicemia due to any organisms may be associated with delirium, stupor and, finally, coma. However, septicemia due to *B. coli* is not ordinarily regarded as an acute fulminating disease, except as an agonal event.

In our cases the patients were struck down with an acute illness, usually with a sudden chill, at a time when they did not regard themselves as ill enough to seek medical attention. From then on the course was rapid. The duration of the disease was from four to five days with the exception of the 1 patient who recovered. The blood cultures were taken either at admission to the hospital or within thirty-six hours. The characteristic clinical picture present in all 4 cases was drowsiness which rather rapidly became coma. Two of the patients manifested narcoleptic phenomena, only 1 showed definite delirium. It seems obvious that sulfanilamide was without effect in 2 of the patients at the stage of the disease at which it was used. In case 3 an effort was made to obtain sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) for intravenous use but the material did not arrive until the patient had died. In case 4 the patient, who had *B. aerogenes capsulatus* in both the blood stream and the urine, was treated with sulfapyridine rather early in the disease and it is reasonable to assume that the treatment was effective.

It is possible that fulminating septicemia due to *B. coli* or related organisms occurs more frequently in patients with uncontrolled diabetes.

² Davis, N. P., and Turner, O. E. Colon Bacillus Septicemia Associated with Calculus Obstruction of the Common Duct. Review of Literature and Report of Case, *Pennsylvania M. J.* **43**: 26-28 (Oct.) 1939.

and infection of the urinary tract. In our patients the dextrose concentrations in the blood varied between 400 and 800 mg per hundred cubic centimeters, almost optimal conditions for the growth of gram-negative bacilli. Kutzman and one of us (B. D. B.³) made a complete urologic survey of 84 unselected cases of diabetes occurring in women between the ages of 36 and 79. We observed *B. coli* or closely related organisms in the ureteral urine either by direct smear or culture in 34 of the cases. Sharkey and Root⁴ likewise called attention to the frequency of *B. coli* infections in the urinary tracts of persons with diabetes.

In considering the problem of immunity Richardson⁵ compared the bactericidal power of the blood for *B. coli* of persons with diabetes with that of normal persons. He noted that the blood of persons with diabetes was but slightly weaker than his normal controls in killing power for that organism. It is conjectured that a sudden invasion of the blood stream occurs in the person with uncontrolled diabetes who has urinary infections. Because large amounts of dextrose are present, multiplication of the organism in the blood stream might occur much more rapidly than in the blood of normal persons, especially if the bactericidal power of the blood serum is impaired.

SUMMARY AND CONCLUSIONS

Four cases are reported in which the patients, all obese women with uncontrolled diabetes, had a fulminating form of septicemia caused by a gram-negative bacillus of the colon aerogenes group. In 3 cases *B. coli* (*Escherichia coli*) was grown from cultures of both the blood and the urine, in the remaining case similar cultures showed the *B. aerogenes capsulatus* (*Aerobacter aerogenes*).

The disease is characterized by an acute onset and a rapid course. It proved fatal with the exception of the 1 patient whose infection was caused by *B. aerogenes capsulatus* and who recovered after treatment with sulfapyridine.

No antemortem diagnosis was made in the first case because the organism found in the blood stream was not identified until after the patient's death. Necropsy revealed chronic pyelonephritis with small capsular abscesses. The clinical observations in the other 3 cases were

3 Bowen, B. D., and Kutzman, N. The Urinary Tract in Diabetic Women. Its Contribution to the Incidence of Hypertension, *Ann. Int. Med.*, to be published.

4 Sharkey, T. P., and Root, H. F. Infection of the Urinary Tract in Diabetes, *J. A. M. A.* **104**: 2231-2235 (June 22) 1935.

5 Richardson, R. Immunity in Diabetes. Influence of Diabetes on the Development of Antibacterial Properties in the Blood. *J. Clin. Investigation* **12**: 1143 (Nov.) 1933.

so similar to those in the first case that the diagnosis was suggested and treatment begun before identification of the organism in the blood stream was possible

The characteristic clinical manifestation was a drowsiness which rather rapidly passed into unconsciousness. Two of the patients manifested narcolepsy of a peculiar type

Although 2 of the patients were regarded as having diabetic coma on admission and were treated for this condition, the facts that diabetic coma is not common in obese patients with diabetes, that these patients were not appreciably dehydrated and that they had high temperatures should have served to distinguish their disease from diabetic coma

PULMONARY STENOSIS WITH BUNDLE BRANCH BLOCK

REPORT OF A CASE WITH SOUND TRACINGS AND SEMISERIAL
STUDIES OF THE CONDUCTION BUNDLE

L MINOR BLACKFORD, MD

AND

FRANCIS P PARKER, MD

ATLANTA, GA

The incorporation of the bulbus cordis into the definitive heart is so often imperfect that among cardiac anomalies defects in the outflow tract of the right ventricle are common. Occasionally, however, after the fundamental structures of the heart have been completed, stenosis of the pulmonary valve develops. This lesion, according to Abbott,¹ is "practically always inflammatory, the result of an endocarditis running its course late in foetal life." White² agreed that pulmonary stenosis is "almost invariably the result of congenital defects."

As already intimated, uncomplicated pulmonary stenosis is rare, in 1,000 cases of congenital heart disease studied statistically by Abbott only 9 cases were listed. Levine³ stated in his chapter on congenital heart disease, "Pulmonary stenosis as an isolated lesion is quite rare." References to uncomplicated pulmonary stenosis associated with bundle branch block have not been found.

Bundle branch block has been the subject of much investigation during the past thirty years. In 1938 this work, of which an important part has been done in the United States, was summarized by Yater.⁴ Emphasizing the scarcity of pathologic studies, he reported 16 cases

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From the Departments of Internal Medicine and Pathology, Emory University School of Medicine

M₁ M B Rappaport, of the Sanborn Company, recorded the sound tracings and interpreted them for us. Dr Everett L Bishop made the photomicrographs.

1 Abbott, M E. Atlas of Congenital Cardiac Disease, New York, American Heart Association, 1936, p 44

2 White, P D. Heart Disease, ed 2, New York, The Macmillan Company, 1937, p 455

3 Levine S A. Clinical Heart Disease, ed 2, Philadelphia, W B Saunders Company, 1940, p 207

4 Yater, W M. Pathogenesis of Bundle Branch Block. Review of the Literature, Report of Sixteen Cases with Necropsy and of Six Cases with Detailed Histologic Study of the Conduction System, Arch Int Med 62 1-96 (July) 1938

with autopsies, in 11, serial sections of the conduction system had been studied histologically. Since 1938 Bischoff⁵ has reported histologic studies of the conduction system in 4 cases, but he has not presented photomicrographs. Certain lines from Yater's admirable monograph may be quoted:

The pathogenic factor in cases of bundle branch block is almost always disease of the coronary arteries, rheumatic or degenerative, or hypertension. The histogenic factor is mainly fibrosis. The vascularization of the conduction system explains well why it is rare for one bundle branch alone to be affected.

In 1928 King⁶ suggested that bundle branch block can often be recognized from physical signs. The most important of these was a bifid thrust of the apex. The auscultatory signs listed were feebleness of systolic heart sounds, reduplication of the first sound at the apex (including presystolic gallop) and asynchronous systolic apical murmurs. Although four of the first five diagnoses made by one of us (L M B) were confirmed electrocardiographically, his subsequent experience has indicated that the percentage of clinical recognition of bundle branch block is no higher than is to be explained by the laws of chance. It is the present consensus that bundle branch block can be proved only by the electrocardiograph. It may be that exact study of the heart sounds will eventually increase the accuracy of clinical diagnosis. For such exact study, especially for demonstration graphic records are necessary. Practical methods of recording the heart sounds synchronously with electrocardiographic deflections have but recently been introduced. The presentation of such records in a case of bundle branch block is thus worth while, even though in the present case the record is complicated by the effects of a pronounced valvular lesion.

Because pulmonary stenosis without other gross structural defects is rare, because sound tracings of hearts studied pathologically are still novelties, because few histologic studies of abnormal conduction bundles have been reported, and because an account presenting these three features in combination does not appear to have been published before, the following case is reported.

REPORT OF CASE

In the course of routine physical examination of college boys in September 1934, C S, aged 18, was observed. Tall, but poorly nourished and poorly developed, he was of the vagotomic type with the subdued manner of a boy who has never been able to run and play and fight. He stated that he had suffered

5 Bischoff, S. Vergleichende electrocardiographisch-histologische Studien an vier Fallen unter besonderer Berucksichtigung des Reizleitungssystems, Beitr z path Anat u z allg Path **103** 183-214, 1939.

6 King J T. The Clinical Recognition and Physical Signs of Bundle Branch Block, Am Heart J **3** 505-524 (June) 1928.

from heart trouble since babyhood. The area of cardiac dulness was greatly enlarged. A systolic thrill was felt along the left border of the sternum, and a harsh systolic murmur was heard, loudest in the pulmonic region. The pulse pressure was low and the pulse rate rapid.

On Sept 16, 1937, an opportunity was afforded for detailed study. His father had died of pneumonia at 54. His mother was in good health. She had suffered no infections during any of her 5 pregnancies, her 4 other children were living and well.

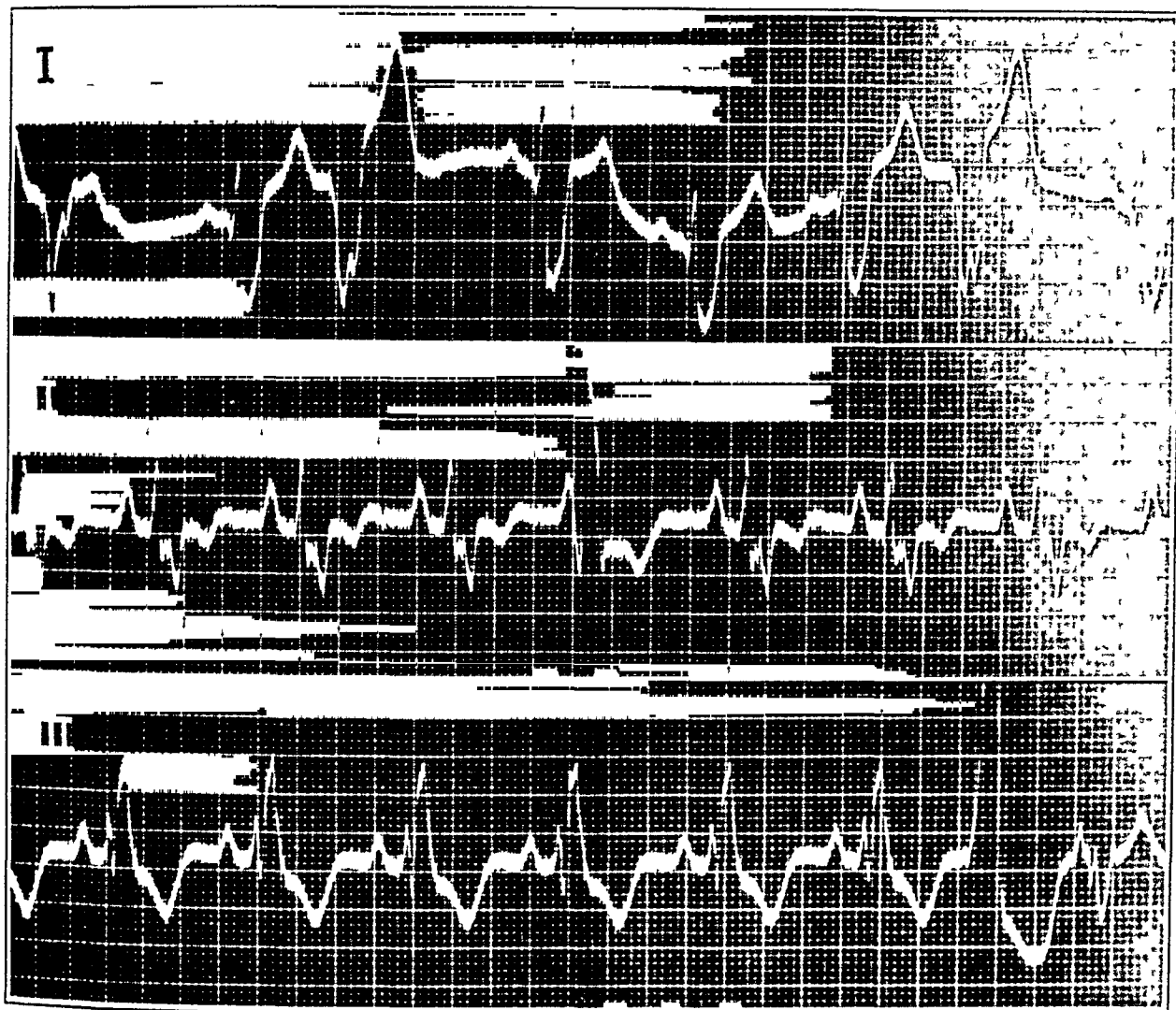


Fig 1—Electrocardiogram taken Oct 7, 1937. The pulse rate is 80. QRS measures 0.18 second. In addition to the right bundle branch block, the electrocardiogram shows 6 premature ventricular contractions, most of which arose in the right ventricle.

C. S. had been delivered uneventfully and was considered a normal baby until an illness at 2, an ailment characterized by fever and difficulty in swallowing. Soon after this a heart murmur was noted for the first time; it was attributed to the recent illness. As a child he could "play catch," but he was not able to run after a ball or engage in more strenuous games. By the time he entered high school, his physical activities were greatly limited, and whatever he did he had to do slowly. When he entered college difficulty in going upstairs interfered

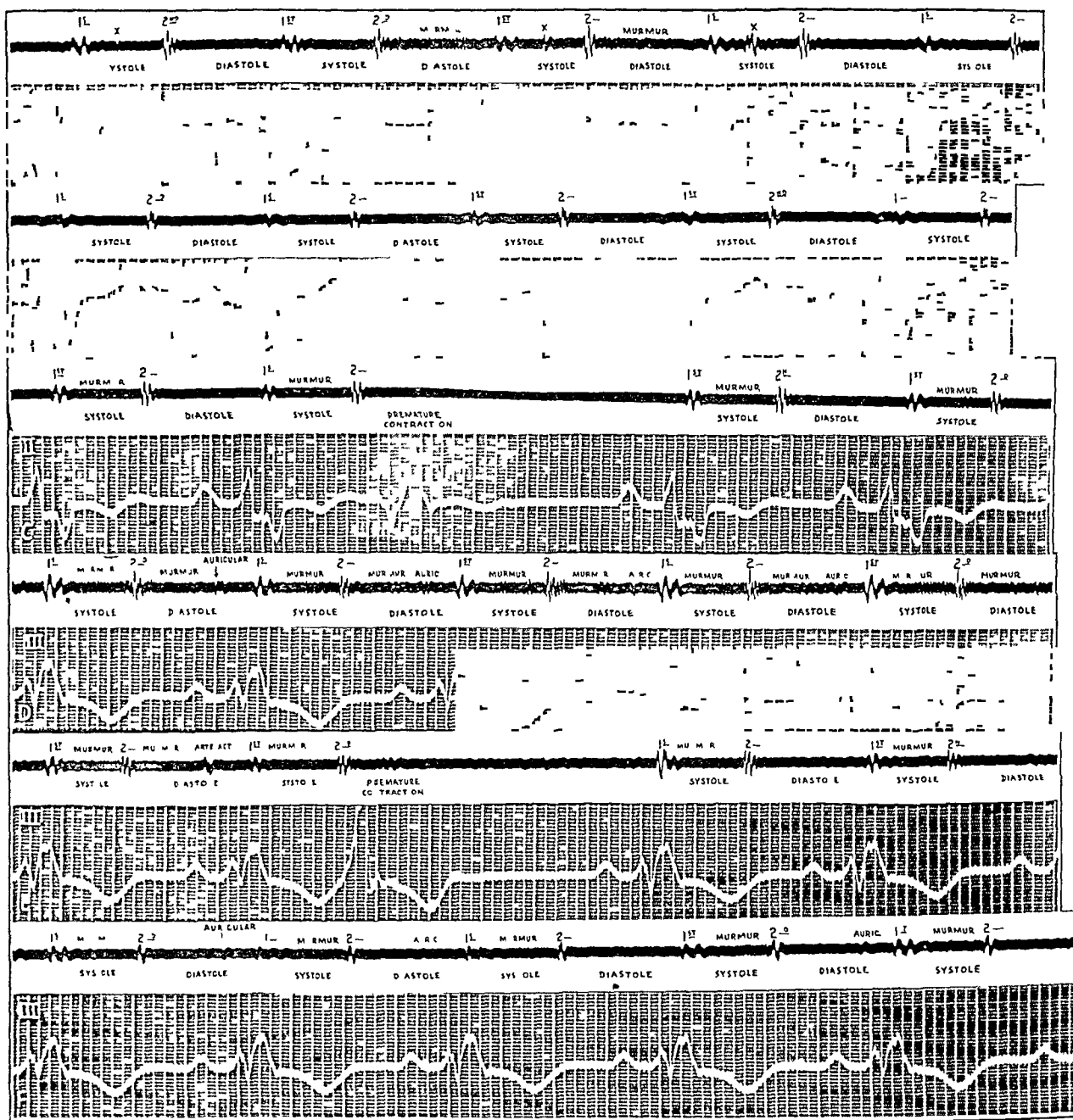


Figure 2

(See legend on opposite page)

his choice of courses. He had, however, been able to work his way through by means of sedentary jobs, especially tutoring. Although he could not walk a block slowly without stopping to rest, he had never noted edema. Cyanosis had not been observed at rest. He had been singularly free of infectious diseases.

At the 1937 examination, C. S. was $72\frac{1}{2}$ inches (184 cm) tall and weighed 130 pounds (59 Kg). He was faintly cyanotic, his hands were clammy, the fingers were slightly clubbed. The neck veins collapsed in diastole. The precordium bulged, and there was a diffuse heaving beat. Cardiac dulness extended out into the axilla, and a systolic thrill was felt along the left border of the sternum. Heart action was irregular. A harsh systolic murmur was heard in the pulmonic region. The blood pressure at rest was usually about 114 systolic

EXPLANATION OF FIGURE 2

A, lead I with the bell in the fourth interspace 5 cm from the midline. There are a low-pitched first heart sound and a higher-pitched second sound, and a very slight systolic murmur. About midway in systole there is an extra heart sound of variable intensity (τ), possibly a systolic gallop. There is also a variable diastolic murmur (lead I).

B, bell in fifth interspace of the anterior axillary line. The first sound is of very low pitch (probably below human audibility), the second is higher pitched and somewhat more intense (lead I).

C, bell at third interspace just to the left of the sternum. There are a fairly low-pitched first heart sound and a somewhat higher-pitched, more intense second sound, and a slight systolic murmur. At the time of the occurrence of the premature contraction no heart sound occurs. A possible reason for the lack of a heart sound during the premature contraction may be that it preceded the time the atrioventricular valves were sufficiently open, that is, the presence of a first heart sound depends on the closure of a previously opened atrioventricular valve. Similarly, the second sound depends on the closure of the previously opened semilunar valves. If the semilunar valves do not open owing to the premature ventricular contraction, the absence of a second heart sound is to be expected (lead II).

D, bell at first left interspace. A low-pitched first heart sound is present, followed by a systolic murmur. The systolic murmur has a tendency to become more intense later in systole but covers practically all of the systolic phase. A second sound of much higher pitch is present, followed by a short diastolic murmur. Also present is an auricular sound, well displaced and prior to the first heart sound. A rather interesting point concerning the systolic and diastolic murmurs is that the major frequency components are the same in both murmurs, the systolic murmur appears to run through the second heart sound to form the diastolic murmur (lead III).

E, bell at second right interspace. There are a very low-pitched first heart sound, a slight systolic murmur, a second heart sound of higher pitch and a very low-pitched rumble (well below the range of human audibility) throughout diastole. A premature contraction accompanied by a slight heart sound is also present (lead III).

F, bell just below the sternoclavicular joint. There are very low-pitched first and second sounds, a medium high-pitched systolic murmur and, trailing the second sound, a soft diastolic murmur (lead III).

and 96 diastolic, the pulse rate was 80. Slight exertion might change the blood pressure to 136 systolic and 76 diastolic and the pulse rate to 120.

Fluoroscopic examination showed a huge heart with enlargement principally to the left and backward. In view of the physical signs of obstruction in the outflow tract of the right ventricle it was thought that this ventricle probably formed the apex. The aorta appeared normal. The pulmonary trunk was greatly dilated.

The electrocardiogram showed right bundle branch block (Bayley's ⁷ group 1) and frequent premature ventricular contractions, arising principally in the right ventricle.

He was graduated in June, 1938. During the following year the requirement of a physical examination several times barred him from professional employment. Although he picked up occasional temporary jobs, especially in tutoring, he grew discouraged and profoundly depressed. He fainted several times and several times feared he would faint, apparently owing to paroxysms of tachycardia.

On April 4, 1939, Mr. M. B. Rappaport recorded the heart sounds synchronously with an electrocardiogram. His interpretations are presented in the legends of the illustrations. In brief, the sound tracings corroborated the presence of a systolic murmur, loudest in the pulmonic area and followed by a short diastolic murmur heard only there.

Six weeks after these records were made, C. S. left home apparently as well as ever. Half an hour later he was found dead in his car. He had pulled up to the curb, cut off the ignition, pocketed the keys and opened the door.

Necropsy.—The postmortem examination (the cranium was not opened) revealed little of interest except in the heart. This organ extended to the left wall of the thorax and almost to the posterior wall, it had crowded the left lung into the upper part of the thoracic cavity. The heart weighed 955 Gm. (according to Smith,⁸ the average weight of the heart of a man of 130 pounds [59 Kg.] is 255 Gm.) The right ventricle formed practically the anterior surface of the heart (fig. 3) and indeed the greater mass of the heart. From the apex to the level of the pulmonary ring the heart measured 15 cm., and across the base, 14 cm. The anteroposterior diameter was 11 cm. The thickness of the wall of the right ventricle in some places was 4 cm., the average thickness of the left was 1.8 cm. The tricuspid ring showed some dilatation, measuring 12.5 cm. in circumference, the leaflets were moderately thickened, but appeared to have been functionally adequate. The pulmonary valve was a tough dome-shaped membrane, measuring around its base about 8.5 cm., in its upper surface was a circular aperture 6 mm. in diameter. Viewed from above (as shown in the inset of fig. 3) three ridges represented fusion of the commissures between the three semilunar cusps. The pulmonary trunk was dilated and thin walled, its inner circumference was 12.5 cm. The mitral valve measured 10 cm., its leaflets were slightly thickened. The normal aortic valve was 6 cm. in inner circumference. The coronary ostia were not obstructed.

The fundamental structure of the heart was normal, there was no anomalous communication between the two sides of the heart. The right atrium was markedly

⁷ Bayley, R. H. The Frequency and Significance of Right Bundle Branch Block. *Am. J. M. Sc.* **188**: 236-242 (Aug.) 1934.

⁸ Smith, H. L. The Relation of the Weight of the Heart to the Weight of the Body, and of the Weight of the Heart to Age, *Am. Heart J.* **4**: 79-93 (Oct.) 1928.

dilated. The right ventricle was even more dilated, especially in the pulmonary conus. This great enlargement of the right chambers resulted in a torsion of the heart with displacement of the interventricular septum backward and to the left. This displacement was so great that a needle passed through the septum at the base of the posterior and lateral aortic leaflets entered the right atrium about 4 cm posterior to the pars membranosa septi rather than through this structure itself. Grossly, the myocardium evidenced a high degree of fibrosis.

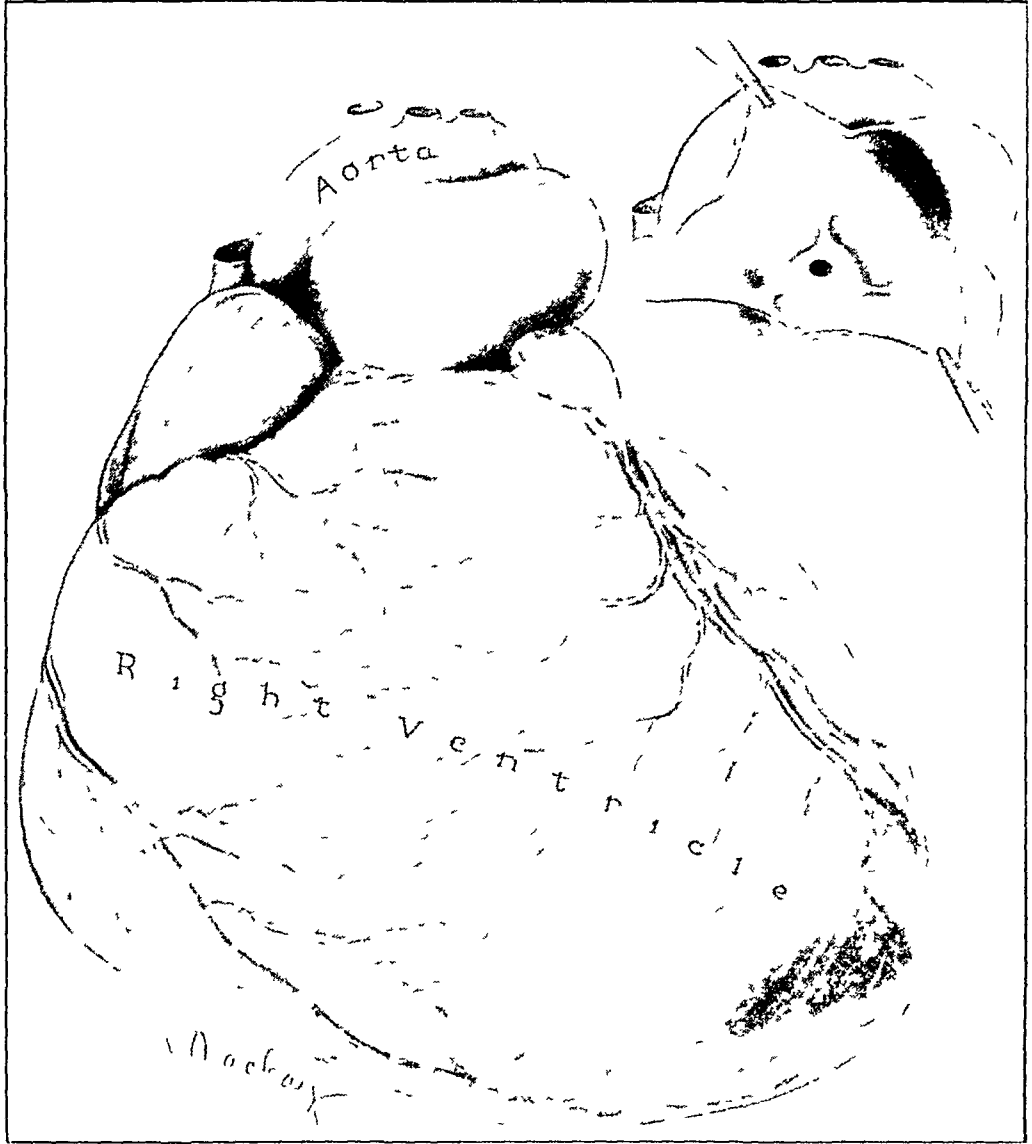


Fig 3—The appearance of the heart. Note the size of the right ventricle and how it forms the apex of the heart. Note also the dilated pulmonary trunk. The inset shows the appearance of the pulmonary valve from above. It is apparent that three semilunar cusps were formed and that they later fused.

Histologic Studies—Tissue from the lower part of the interatrial septum extending down toward the interventricular septum and including the pars membranosa was removed and cut into 3 equal blocks. Microscopic sections were taken from each block at intervals of approximately 60 microns to show the conduction bundle longitudinally (see fig 4A).

A number of the sections showed the main bundle throughout most of its length down to the point where it divided just above the pars membranosa. Microscopic evidence of considerable damage was present. Variation in the staining of the

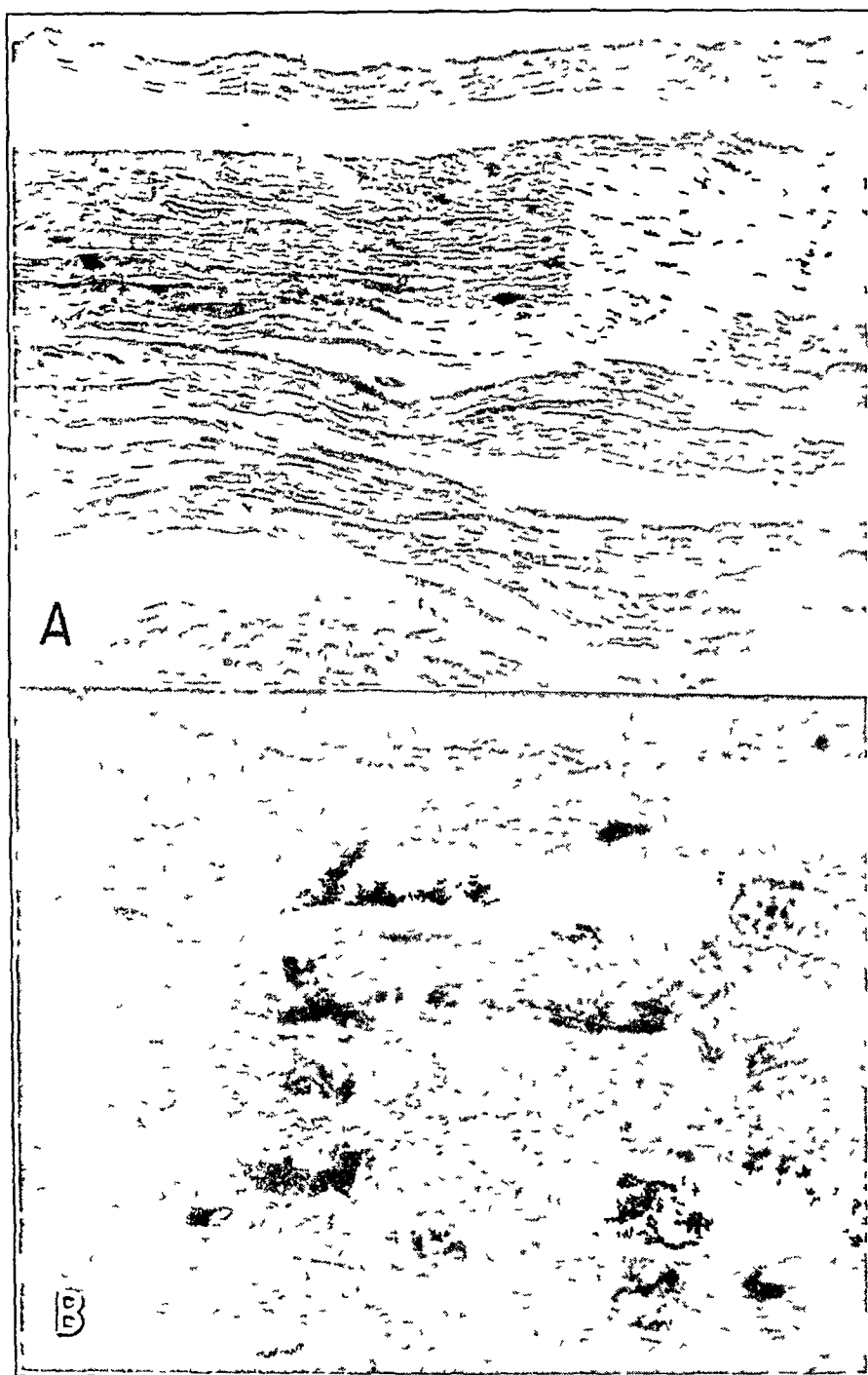


Fig 4—*A*, low power photomicrograph showing a longitudinal section of the main conduction bundle immediately proximal to the pars membranosa. Hematoxylin and eosin stain, $\times 150$. *B*, higher power photomicrograph of a part of *A* showing light-staining areas of granular degeneration and dark homogeneous areas resembling Zenker's hyalin. Hematoxylin and eosin stain, $\times 600$.

muscle fibers gave the tissue a mottled appearance. The darker areas exhibited a loss of striation, causing a homogeneous appearance suggestive of Zenker's hyaline degeneration. The lightly stained portions showed definite granulation.



Fig 5—*A*, low power photomicrograph showing an area of ischemic necrosis in the upper part of the interventricular septum. There is complete destruction of the myocardium with chronic inflammatory and fibroblastic reaction. Hematoxylin and eosin stain, $\times 150$. *B*, high power photomicrograph of an artery in the upper part of the interventricular septum. The lumen is narrowed by subintimal proliferation. The dark spots throughout the vessel wall are pigment deposits. Hematoxylin and eosin stain, $\times 600$.

(fig 4 B) There was also variation in size and staining character of the nuclei, some were markedly pyknotic. No actual replacement of the bundle by fibrous tissue could be demonstrated. These changes were most pronounced in the portion of the bundle just proximal to its bifurcation at the pars membranosa. The amount of damage to the tissue in the muscle bundle appeared sufficient to cause the defect of conduction.

In sections from other parts of the heart, particularly in those from the upper part of the interventricular septum, the cardiac muscle showed diffuse fibrosis. This fibrosis had resulted in loss of muscle tissue and definite abnormality of that which remained. In some areas inflammatory infiltration, mainly by mononuclear and large phagocytic cells but with a few eosinophils, was noted (fig 5 A). In one place there was a distinct foreign body giant cell reaction. These lesions showed none of the characteristics of a tuberculous reaction, nor were they the type seen in the Aschoff body. The appearance was more that of active regeneration of fibrous tissue in an area of destroyed cardiac muscle.

The arteries showed thickening of the walls with subintimal proliferation and narrowing of the lumen. Heavy deposition of brown granular material, apparently blood pigment, was seen in the arterial walls (fig 5 B).

COMMENT

Abbott's¹ account of congenital pulmonary stenosis might have been written to describe the case of C S.

In these uncomplicated cases the right ventricle is always the seat of a marked simple hypertrophy and the right auricle dilated, but the heart is otherwise normal.

Such cases are much less frequent than the developmental type of pulmonary stenosis with associated ventricular septal defect and dextroposition of the aorta, but the circulatory conditions are more favorable in that the chief (and with closed foramen ovale, the only) cause of raised oxygen-unsaturation is retardation of flow with increased deoxygenation in the capillaries. Cyanosis is therefore usually moderate in degree and of relatively late onset, frequently not appearing until after early childhood. The condition tends, too, to become progressive. There may be an enlarged pulmonary arc from dilatation of the pulmonary trunk above the valve, and right predominance is a marked feature of the electrocardiogram.

The clinical diagnosis in this case was congenital pulmonary stenosis, probably associated with some other anomaly. As Abbott noted, uncomplicated pulmonary stenosis is less common than "the developmental type of pulmonary stenosis associated with ventricular defect and dextroposition of the aorta." This complex ("tetralogy of Fallot" or "biventricular aorta with pulmonary stenosis") is the most common cause of deep lifelong cyanosis in an adult. It could not of course explain the case of C S, because the cyanosis and clubbing were both mild, the ascending aorta was not dilated, and the pulmonary trunk was dilated.

⁹ Blackford L M, Davenport, T F, and Bayley, R H. Right Aortic Arch. I. Clinical Report of a Case with Associated Anomalies, *Am J Dis Child* 44: 823-844 (Oct) 1932.

Blackford and McGehee¹⁰ noted in 1933 that in the majority of cases of congenital heart block the clinical diagnosis is patent interventricular septum. At the time of that report a review of the literature showed that "this defect was present in the 5 patients that came to necropsy. The atrioventricular bundle studied microscopically in 3 was imperfectly developed." It seemed reasonable then to conclude that in cases of congenital heart disease interference with the conduction system was a result of imperfect development and that this was associated with a defective interventricular septum. Therefore, in the case of C. S. the interference with conduction was interpreted as evidence in favor of a defect in the muscular part of the interventricular septum.

The illness in infancy raises a possible doubt. It is not improbable that C. S. never had a physical examination prior to that illness and his mother may have exaggerated the importance of the ailment. It is quite possible too that she experienced an acute infection a few months before the child was born and twenty-four years later had forgotten it. The valvular lesion appeared to be the late result of an inflammatory process, one thing we can be sure of is that this infection occurred after the fundamental structures of the heart had been completed. However, Lewis¹¹ described congenital pulmonary stenosis as follows: "Pulmonary stenosis of simple form is a very rare condition in which a strong membranous partition perforated centrally by a small circular aperture is found at the origin of the pulmonary artery." It is our present opinion that this infection was prenatal.

Since the left ventricle did not come in contact with the anterior wall of the chest, a bifid apical thrust could not be seen or felt. The sound tracings indicated that the first sound was not audible at the apex, but they did not show reduplication, gallop or asynchronous murmurs. Bundle branch block, in our opinion, could not have been diagnosed in this case without the electrocardiogram.

The histologic studies indicated that the changes in the myocardium were the result not of chronic inflammation but of ischemia. This ischemia seemed to have been caused by mechanical factors involved in the distortion of the interventricular septum secondary to the tremendous hypertrophy of the right ventricle required to overcome the resistance of the 6 mm. pulmonary orifice. At the same time it must be admitted that the thickening of the arterial walls may have interfered to some extent with the blood supply. The histologic studies of the conduction system did not include the two branches. Such studies seemed unneces-

10 Blackford, L. M. and McGehee, H. M. Congenital Heart-Block. A Case with Other Cardiac Anomalies in a Student of Twenty-Three Years. *Am Heart J* 9:96 (Oct.) 1933.

11 Lewis, T. *Diseases of the Heart*, ed. 2. New York, The Macmillan Company, 1937, p. 266.

sary, for Yater's work is generally accepted as conclusive. In short, our studies support the opinion of Yater and of Bischoff, as well as of earlier writers, that bundle branch block is usually due to interference with the blood supply to the septum.

The histologic examination of the myocardium emphasized a point of clinical importance. Paroxysms of tachycardia occur frequently in persons with normal cardiovascular systems and in such persons, once the diagnosis is made, are rarely worthy of any concern. One is therefore apt to forget that attacks of rapid heart action are more common in diseased hearts than in normal hearts and that when they speed up a seriously damaged heart, the outlook is grave, as was emphasized recently.¹² In this case it seems quite possible that the paroxysms of tachycardia were ventricular in origin, and that the patient died in such a paroxysm. In retrospect, therefore, his death might have been expected at any time during several months.

The depression that C. S. experienced after graduation has been noted. The disappointments he experienced seemed at the time to offer adequate explanation, but one may wonder now if his depression was not more the result of an ill defined sense of impending death.

SUMMARY

A case is presented of pulmonary stenosis with right bundle branch block occurring in a man who died at 23. Congenital pulmonary stenosis was diagnosed several years before his death, but the electrocardiogram was interpreted as evidence of a septal defect.

Sound tracings lent little support to the opinion that bundle branch block can be diagnosed with the stethoscope.

Histologic studies confirm the thesis that the cause of bundle branch block is often interference with the blood supply of the interventricular septum.

Paroxysms of tachycardia in cases of serious heart disease indicate a grave prognosis.

¹² Blackford, L. M. Mitral Stenosis as a Cause of Angina Pectoris, *Am Heart J* 20 492-497 (Oct.) 1940.

SYNDROME OF DESTRUCTION OF THE PINEAL GLAND

EXPERIMENTAL AND CLINICAL OBSERVATIONS

JOHN MARTIN, M D

AND

LOYAL DAVIS, M D

CHICAGO

Among those organs of the body the physiology of which still remains incompletely understood, no one structure has caused more diversity of opinion or argumentative disagreement than has the pineal gland. It has been studied anatomically in almost every branch of all the vertebrates, since the turn of the present century all manner of physiologic experiments have been performed in the attempt to prove or disprove its endocrinal potentialities, and, recently, pineal substance and so-called pineal extracts have been used hopefully in opotherapy. Overenthusiasm to disclaim or substantiate a physiologic function for the pineal gland, on the one hand, has been balanced by the attitude of neglect, confusion or evasion, on the other, the net result being a voluminous, rambling, bewildering and unconvincing literature.

The preponderant anatomic evidence at hand indicates the glandular possibilities of the pineal gland in the early stages of life in most vertebrates, though this will not be conceded to be true by all neuro-anatomists¹. Extensive and carefully performed phylogenetic investigations do not support the theory that the pineal gland in mammals is a remnant of the reptilian midline eye². Anatomic facts alone are insufficient for a complete understanding of the physiologic significance of the pineal gland, more recent studies have been concerned with the physiologic action of pineal products in immature animals, the relation of such secretions to the known glands of internal secretion and the part played,

From the Division of Surgery, Northwestern University Medical School, and the Cushing Tumor Registry, Yale School of Medicine.

1 Rio-Hortega, P. The Pineal Gland, in Penfield, W. Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 2.

2 Tilney, F., and Warren, L. F. A Contribution to the Study of the Epiphysis Cerebri with an Interpretation of the Morphological, Physiological, and Clinical Evidence, American Anatomical Memoirs, Philadelphia, Wistar Institute of Anatomy and Biology, 1919, no. 9. Tilney, F. The Pineal Gland, in Cowdry, E. V. Special Cytology, New York, Paul B. Hoeber, 1928, vol. 1, p. 503.

if any, in the maturation of the individual animal. Extirpation or implantation of the gland and the administration of pineal substance have been the paths of approach used by physiologists. That the results of these studies have varied widely, conflicted and given no final solution hardly needs to be emphasized here. Tumors of the pineal gland alone in human subjects, or in conjunction with pathologic processes in the adrenals, gonads or hypothalamus (including the pituitary), have led clinicians into a state of doubt and indifference.

The time of the preparation of the present report (July 1940) marks the end of a four and a half year period during which the experimental phase of our investigations has had to do with the extirpation of the pineal gland in rats, cats, dogs and monkeys. Implantation of the pineal gland or the administration of pineal substance or extract has not yet been carried out, for it was our primary aim to observe in a conclusively large enough series of animals the effects of destruction of the pineal gland alone (apinealism) early in life, when there is actual histologic evidence of glandular function. All pinealectomized animals were controlled by litter mates of the same sex, both lesion and control animals were reared under equal and standard laboratory conditions and a complete life history was recorded for each animal. We have been concerned with the growth and maturation, both somatic and sexual, in animals of both sexes from which the pineal gland was removed at an early age. We have tried to evaluate those changes in behavior which have been unquestionably present, and we have compared the reproductive cycles of the pinealectomized animals with those of their normal litter mates.³ In addition, we have compared the histologic characteristics of many of the organs of the pinealectomized animals with those of their controls, and animals which have been castrated or hypophysectomized or both are now being reared in the laboratory to show what the effect of such treatment may be on the histologic development of the pineal gland at various ages. A minor portion of our histologic observations has already been reported³ and the completed report will be forthcoming at a suitable time.

This communication has to do with certain of our data obtained on animals which we believe should be presented in conjunction with the results of an analysis of a large series of tumors of the pineal gland in human beings.

Cats have been used extensively in our investigations because, for several reasons they are well adapted to such use. The cat skull offers no surgical difficulties, the cat has a well developed mammalian brain, with definite and easily recognized landmarks, the cat is well up in

3 Davis, L., and Martin, J. Results of Experimental Removal of Pineal Gland in Young Mammals, *Arch Neurol & Psychiat* **43** 23-45 (Jan) 1940

the phylogenetic scale, and litters are usually of such size as to allow at least 2 lesion animals and 1 control of one sex in each litter. Furthermore, the cat is an inexpensive animal to maintain, and it is well adapted to laboratory life. Because of the facility with which accurate lesions may be made in the cat brain with the aid of the Horsley-Clarke stereotaxic instrument, the cat seemed especially useful, and the great majority of our animals have been pinealectomized by this means.

At the present time 108 cats have been studied, of which 68 were males and 40 were females. All except 6 were successfully pinealectomized with the Horsley-Clarke instrument. Four cats were pinealectomized by means of retracting the cerebral hemisphere, splitting the splenium of the corpus callosum and plucking out the gland, but all of these animals died within a few days of their operation. The average age of the kittens at operation was $6\frac{1}{2}$ weeks, and autopsy studies have been completed on cats killed at periods varying from immediately after operation to thirty-five months later.

At the time of operation the kittens were numbered, classified as to sex, weighed, measured from crown to rump, given a roentgen examination and photographed, several were given an injection of 1 cc of 2 per cent aqueous solution of alizarin red to indicate the rapidity of bone growth, since the dye is deposited by the periosteum in ring formation in the cortex of growing bones. With the kittens under anesthesia induced by phenobarbital sodium, the scalp was shaved, cleansed and surgically opened over the vertex. After careful placement of the Horsley-Clarke instrument, a small burr hole was made in the skull over the midline, and, according to predetermined coordinates, a small electrode, insulated except at the tip, was passed through the sagittal sinus, along the falx, through the splenium of the corpus callosum and into the pineal gland. Adequate galvanic current was then used to coagulate and destroy this structure. The skin was closed with clips, and the animals were allowed to recover in a warm box. They were able to eat and drink within twenty-four hours, and there was no instance of infection of the wound following the operation. Weekly weights and measurements were recorded, behavior characteristics showing any variation from the normal were observed, all illnesses and feeding difficulties were noted, and roentgenograms, photographs and injections of alizarin were repeated at definite intervals.

There were no significant differences in the somatic development of the control and the pinealectomized female cats, but when the entire series were reviewed and the time of the first estrus noted, it was found that the normal female cats experienced estrus at an earlier date than did their pinealectomized mates. Control females mated with pinealectomized males produced small litters of no more than 4 kittens which were usually feeble, often dying of starvation after twenty-four to forty-eight

hours because of their inability to nurse. The pinealectomized mothers likewise had small litters which they tended to drop three or four days before term with the kittens dead or, if alive, frequently too feeble at birth to nurse properly. Only 3 pinealectomized mothers had an adequate supply of milk, the others showing slight or no breast changes at parturition and responding only moderately to injections of prolactin. In most instances the pinealectomized mothers showed but little maternal instinct, frequently ignoring their kittens for hours, covering them with straw and making few attempts to encourage the kittens to nurse. Two such mothers failed to dispose of the placentas and to disengage the newborn litter from the entangled cords and membranes. We have

TABLE 1—*Average Weights and Lengths (Crown-Rump) at Various Critical Periods*

	Control	Lesion Animal
A Male cats		
At operation, approximately 6½ weeks of age		
Weight	838 Gm	830 Gm
Length	26.0 cm	25.6 cm
Nine months of age		
Weight	2,226 Gm	3,118 Gm
Length	40.1 cm	45.5 cm
Complete adult status, approximately 15 months of age		
Weight	2,900 Gm	3,656 Gm
Length	42.5 cm	46.4 cm
B Female cats		
At operation, approximately 6½ weeks of age		
Weight	709 Gm	727 Gm
Length	26.7 cm	25.6 cm
Nine months of age		
Weight	2,381 Gm	2,490 Gm
Length	41.1 cm	41.3 cm
Date of first estrus (see table 2)		
Weight	2,650 Gm	2,701 Gm
Length	42.6 cm	42.4 cm

found it much more difficult to rear the kittens of pinealectomized cats than those of normal cats.

The average normal male cat shows no sexual interest before 13 or 14 months of age, and until 8 or 9 months of age our male cats all showed much the same behavior. But at the age of approximately 9 months the pinealectomized male cats began to be less playful, exhibited sexual interest in female cats, were heavier and had a larger skeleton than did their controls. They had larger external genitalia than did their controls, had frequent erections and were sexually potent. Growth continued in both the control and the lesion animals until the age of 15 or 16 months, but when growth had ceased and all the animals were mature, the lesion animals were in every instance larger. All significant organs were removed at autopsy, weighed fresh and studied histologically.

Tables 1 and 2 indicate the growth and sexual development of the cats used in this study and make evident the following facts: 1. At the

age of 9 months the pinealectomized male cats were sexually mature and were longer and heavier than their normal controls. 2 When complete body growth was attained in both lesion and control animals, the lesion animals were notably the larger. 3 There were no important differences in the somatic development of the female cats. 4 The pinealectomized female cats experienced their first estrus at a later date than did their normal controls.

Second generation cats, the offspring of certain of the cats with which the foregoing data are concerned, have been reared with innumerable difficulties and with a high mortality in the early weeks of life. Thirty-seven male and 16 female second generation cats have been born. As previously noted, they were in most cases weak and undersized at birth, grew slowly and got off to a slow start in early life.

TABLE 2—*Data Indicative of Sexual Maturity*

Average breeding age	
Male controls	14.0 mo
Male lesion cats	9.6 mo
Average age at which first estrus appeared	
Female controls	11.9 mo
Female lesion cats	14.8 mo

TABLE 3—*Data on Second Generation Cats*

	Male	Female
Born dead	4	1
Lived 1 week	9	3
Lived 8 to 35 days	8	4
Lived 1 to 3½ months	8	8
Now living, various ages up to 1 year	8	0

They contracted infections of the eyes and sinuses in spite of constant vigilance and special care. They were reared side by side with kittens born to mothers brought pregnant into the laboratory, and the litters of the latter have thrived, while those of the pinealectomized parents did not. Table 3 furnishes some indication of the rate of their early mortality.

Eight male and 2 female cats of the second generation have been operated on, all with litter mate controls. Now living are 2 male controls, 4 male pinealectomized kittens and 2 cats which were controls of lesion litter mates which died early. This, of course, is too small a series to offer any conclusive data, but it may be stated that the pinealectomized males are already showing gains in weight and length over their controls, similar to those seen in the early months of development of their ancestors.

Two male dogs (litter mates) and 2 female dogs (litter mates, but not related to the males) and 3 second generation pups are now under observation. The lesion animals were pinealectomized by manual removal

of the gland through a small craniectomy after the splenium of the corpus callosum had been incised. The male dogs were operated on at 5 weeks of age, the females, at 6 weeks. Complete life histories of these animals have been kept, with records of weight, skeletal growth, sexual development and behavior characteristics. Table 4 indicates the manner in which the pinealectomized male dog outstripped his control in both growth and sexual development and the little developmental difference in the 2 female animals. However, at 17.5 months of age the normal female dog experienced her first estrus, mated and after a normal period of gestation littered 1 female and 2 male pups. The pinealectomized female dog has not yet shown any signs of estrus (at 20 months of age) a delay in development similar to the late appearance of estrus in the pinealectomized female cats.

The results of our investigations on rats have been reported elsewhere.³ Briefly stated, those results showed an increased somatic development in the male animals, no particular difference in growth in the female animals and the histologic evidence of puberty in all animals at the age of autopsy, 90 days. Three male and 2 female *Macacus rhesus* monkeys are now being studied in the laboratory.

In the files of the Cushing Tumor Registry, at the Yale School of Medicine in New Haven, Conn., there are the histories of 18 patients whose cases are classified under "tumors of the pineal gland." Every case was verified by operation or autopsy or both, the clinical records are complete in detail, and in every instance complete and careful histologic reports of the surgical and autopsy specimens are available. For these reasons an analysis of the symptoms of these 18 patients should furnish reliable information concerning the pineal syndrome in man.

Such a detailed analysis has recently been made, and in this review not only were surprising facts revealed concerning changes in somatic and sexual maturation, but it was apparent that collectively the patients presented a pattern of symptoms that occurred in a more or less constant chronologic order and that, when summarized, appeared to constitute a "typical" pineal syndrome, which might conveniently be illustrated by a hypothetical case history. Such a hypothetical case could be substituted with no sacrifice of accuracy for any one of several of the histories in the verified series. It was found that three periods are usually distinguishable in the history of the patient with a tumor of the pineal body. Headache is consistently the first symptom to appear, and it antedates the other, more localizing, symptoms by several weeks, during which time there is a general decline in the patient's condition. The second period is usually ushered in by blurring of vision, diplopia, change in mental outlook, ataxia, increasing drowsiness, permanent changes in the pupils, transient convulsions, disturbances of the heat and water meta-

bolism-regulating centers and, finally, permanent paralysis of the various extraocular muscles, especially those having to do with conjugate upward gaze. In the final stage, during which the patient may first come under careful observation, papilledema or optic atrophy, marked weakness, varying degrees of spasticity, a low temperature and a low basal metabolic rate appear. Air injection studies reveal the typical displacement of the ventricles and advanced internal hydrocephalus, associated with destruction of the walls of the third ventricle.

The symptoms of somatic and sexual precocity must be considered separately, for tumors of the pineal gland may, of course, appear so late in life that precocity is not a point for consideration. In the Cushing

TABLE 4—*Weights and Lengths (Crown-Rump) at Various Critical Periods*

	Age	Category	Weight, Lb	Length, In
A Male dogs	5 wk	Control	3.5	9.9
		Lesion	3.5	10.2
	3 mo	Control	6.8	16.1
		Lesion	11.0	19.5
	8 mo	Control	20.5	23.5
		Lesion	29.0	26.3
	Lesion dog sexually mature at 8 months of age			
	11 mo	Control dog sexually mature at 11 months of age		
	20 mo	Control	23.0	24.5
		Lesion	34.0	27.5
B Female dogs	6 wk	Control	4.5	12.6
		Lesion	5.3	13.0
	3 mo	Control	9.0	17.25
		Lesion	10.0	18.0
	8.5 mo	Control	14.75	21.75
		Lesion	16.75	22.0
	17.5 mo	First estrus of control, followed by normal pregnancy and delivery of 3 pups		
	20 mo	Control	16.75	22
		Lesion	16.75	23
	No evidence of estrus in pinealectomized female			

series there are 11 pinealomas, 4 pineoblastomas, 1 teratoma and 2 ganglioneuromas, 1 of which also showed multilocular cystic degeneration of the pineal body. Fourteen patients were males and 4 were females. Four boys, aged 3, 7, 9 and 12 years, presented cases of pubertas praecox in a moderate to a marked degree, and this is borne out not only by the somatic and sexual maturation in advance of their chronologic age, but also by microscopic study of the testes in those cases in which a complete autopsy was done. According to Dr. Cushing's note, there was "multilocular cystic degeneration of the pineal gland" coupled with a "massive firm tumor of the third ventricle" (a ganglioneuroma) in the 7 year old boy, whose symptoms of precocity, incidentally, were quite evident at birth, but in the other 3 boys of this group there was a primary tumor of the pineal gland.

Sexual precocity was suspected in a lad of 6 years, and another patient, aged 17 years, was said to have shown unusually strong libido on attaining puberty, at the age of 14 years. Somatic precocity was evident in the 4 boys aged 3, 6, 7 and 12 years, since their musculature and body form were in advance of that usual for their age. Mental precocity was a prominent symptom in 2 of these boys who were both physically and sexually precocious. Of the 14 male patients, then, ranging from 3 to 40 years of age, all 5 of those 12 years of age or under showed definite evidence of somatic or sexual precocity or both.

Two adolescents, aged 13 and 20 years, suffered from sexual dystrophy and regressions of sexual characteristics once well developed, but there were no somatic changes other than the usual emaciation. These patients were first seen in the advanced stage of their disease, and autopsy revealed in 1 case that tumor was seeded into the walls of the third ventricle and infundibulum and in the other that solid tumor tissue extended from the pineal gland into the anterior portion of the third ventricle.

Three adult male patients were married, but none had any children. All were considered to be sexually potent, but 1 man had been married only three and a half months. Apparently, in these 3 patients the onset of the disease was well after the attainment of puberty.

The 4 female patients were aged 10, 13, 15 and 29 years. Amenorrhea was present in all 4 patients, but the 29 year old woman had been married two years and had a 6 month old, normal child. A female patient, aged 19 years, in our own series likewise suffered from amenorrhea. There was no evidence of somatic or sexual precocity in any of these female patients, and the amenorrhea was the only evidence of sexual dystrophy in the subjects older than the 10 year old, prepuberal girl.

In addition to these facts concerning body growth and sexual maturation other interesting data came to light in this analysis. Polydipsia or polyuria alone or together was present in 8 patients, and 1 patient, a girl of 15, suffered polyphagia, especially for sweets. Six patients consistently had subnormal temperatures, 10 patients showed loss in weight and generalized cachexia, while the 2 girls aged 13 and 15 showed some gain in weight during the last seven months of life. Terminal apathy and somnolence were marked in all but 4 patients, pigmentation of the skin occurred in 4 patients, 6 patients were definitely hypotensive, and the 4 patients for whom basal metabolic readings had been recorded showed values ranging from -24 to -38 per cent. These more critical laboratory data were obtained during the late stages of the disease, when apparently hypothalamic-hypophysial dysfunction had resulted from advanced invasion by the tumor or from pressure destruction of those structures.

It is generally conceded that disease of the diencephalon produces changes the results of which may cloud, rather than elucidate, the function of that part of the brain, and there is certain to be a great overlapping of symptoms in the presence of an old or a large tumor of the pineal gland which causes destruction of the vegetative centers of the diencephalon. Certainly, in many of the 18 cases of tumor studied there were unmistakable pathologic changes extending beyond the pineal gland itself. The pituitary body, the walls and floor of the third ventricle and the periaqueductal gray matter are, of necessity, injured by a large or "seeded" tumor of the pineal body. Obviously, the solution of the function of the pineal gland does not lie in an analysis of the symptoms found in patients who have suffered from destruction of other areas which are as important as the pineal gland. This solution must come from the recognition of the changes which follow destruction of the pineal body alone, without the occurrence of additional damage to the brain. Teratoma of the pineal gland is primary and present at an early age, and it is, in the majority of cases, accompanied by signs of precocious development. But that teratoma is the sole cause of precocity, as has at times been reported, is certainly not supported by the evidence from the tumors in the Cushing series. It is impossible to say whether all 5 of the male patients with evidence of premature development, and seen for the first time when their disease was well advanced, had signs of such precocity when the tumor of the pineal body was small, local and without hypothalamic or hypophysial effects of a mechanical nature, though it does appear from the case histories that such signs of early maturation were the first to appear in those patients whose early history was recorded. It is worth noting that developmental changes are not particularly common when obstruction and pressure destruction are caused by a lesion, for example in the posterior fossa, in the absence of pathologic changes in the pineal body, it would seem that destruction of the diencephalon by pressure from obstructive hydrocephalus alone is not sufficient to cause such changes in maturation, regardless of the source of the obstruction. Large tumors of the pituitary gland, craniopharyngioma, cyst of the third ventricle, basilar meningioma and other tumors which cause local destruction of the walls and floor of the third ventricle certainly do not commonly produce somatic and sexual precocity in the young patient.

None of our animals in which there was destruction of the pineal gland at an early age showed any polydipsia, emaciation, polyuria, obesity, somnolence, hypothermia, stupidity or infantilism, such as was seen in the patients who had not only a tumor of the pineal body but also widespread destruction of the walls and floor of the third ventricle. As in the patients, early somatic and sexual development were noted only in the male animals with a corresponding maturity of behavior.

None of these animals at autopsy showed any evidence of hydrocephalus, atresia of the aqueduct of Sylvius or destruction of the hypothalamus. In keeping with the less prominent somatic changes in the female patients, our female pinealectomized animals showed no premature body growth. Amenorrhea in the female patients may be compared with the delayed appearance of the first estrus in our pinealectomized female animals and their subsequent variations from the normal reproductive activity.

Thus, it appears to us not too optimistic to compare the results of apinealism in a large series of experimental animals and the corresponding pertinent data relative to sexual and somatic maturation in a large series of cases of tumor of the pineal body in human subjects. No claim is made that the two sets of data tally, fact for fact, for, on the one hand, there was simple, primary destruction of the pineal gland in a laboratory animal, while, on the other, the destruction in man was attended by secondary changes which prevent the attempt to read into the symptoms the answer to the question of the function of the pineal gland. There can be no question concerning the implications of the findings in both the laboratory and the clinical subjects, however, and it is especially indicated that the syndrome of destruction of the pineal gland alone and the effects of resultant endocrine-like changes will most likely be found in the experimental laboratory, to be supported and corroborated by carefully managed clinical investigations.

VITAL CAPACITY OF THE LUNGS IN MIDDLE AGE

RESULTS OF PERIODIC EXAMINATIONS OF MEN OF SEDENTARY OCCUPATION

JOHN H. ARNETT, M.D.

Associate Professor of Medicine in the University of Pennsylvania Graduate
School of Medicine, Chief of Medical Service B, Hospital
of the Protestant Episcopal Church

PHILADELPHIA

The vital capacity of the lungs is the amount of air which can be exhaled after the deepest possible inspiration¹. Obviously, any disease which encroaches on the parenchyma of the lungs (pneumonia, congestive heart failure, etc.) or which interferes with the normal movements of the bones or muscles involved in respiration (immobility of the ribs, paralysis of the phrenic nerve, etc.) or which prevents the free movement of air in the respiratory passages (bronchogenic carcinoma, asthma, etc.) will diminish the vital capacity. That these conditions, as well as numerous others, actually do diminish the vital capacity has long been recognized, and the test of vital capacity would no doubt be a widely used diagnostic office procedure today if the patient could only tell the examiner as much about his vital capacity as he can about his weight. Most patients know what they weighed a year ago and how their weight varies from season to season. Such is not the case with the vital capacity. Seldom does one encounter the patient who can tell the examiner what he "blew" last year, and never one who can give information regarding variations in his vital capacity. Attempts to overcome this handicap have resulted in the construction of formulas for predicting the vital capacity from the height, weight, age and other factors known to influence the vital capacity. Such formulas have their value, just as weight tables have, but are subject to grave limitations. One person may be 15 per cent below the standard and yet be in perfect health, while another may be above the standard and yet have pulmonary tuberculosis. For this reason the test has largely been discarded as a diagnostic procedure.

In certain groups, however, it is possible to secure periodic readings of vital capacity in health to serve as a basis for comparison with readings secured during any illness which might later occur. I have used the test of vital capacity in this manner with satisfaction in the Student Health Service of Drexel Institute of Technology for the past ten years.

¹ Hutchinson, J. Med-Chir. Tr., London 29 137, 1846

To subject the impressions of this procedure to statistical scrutiny, the records of 100 male and 100 female college students over a period of three or four years were analyzed by Arnett and De Orsay² Each student's tendency to gain or lose could be represented by his "best straight line," sloping upward or downward as the case might be The magnitude of individual variations from such a line would then have to be taken into account in interpreting any readings observed during illness It was found that the variations were not large enough to interfere with the usefulness of the test in the diagnosis of diseases accompanied by a pronounced fall in the vital capacity—pneumonia, for example—but that about one third of the students exhibited standard deviations of sufficient magnitude to render the test of questionable value in the diagnosis of conditions in which slight losses in vital capacity were to be expected—early tuberculosis, for example

METHOD

The need for a similar study on persons of middle age becomes obvious, since it has never been determined whether the vital capacity is less variable or more so at this time of life The present study was, therefore, made on men of sedentary occupation who presented themselves annually for a health examination The latter included a complete history, physical examination, urinalysis, blood count and electrocardiogram Roentgenograms of the chest were made when indicated The group, therefore, constituted an ideal one for the purpose of this study I made determinations of the vital capacity at the time of each annual examination, using the same spirometer throughout, the usual technic employed entailed at least three trials for each determination Persons exhibiting a fall in vital capacity attributable to demonstrable causes, such as myocardial or pulmonary disease, have been omitted from consideration The mean age at the time of the first examination was 48.7 years, the oldest man being 66 and the youngest 31

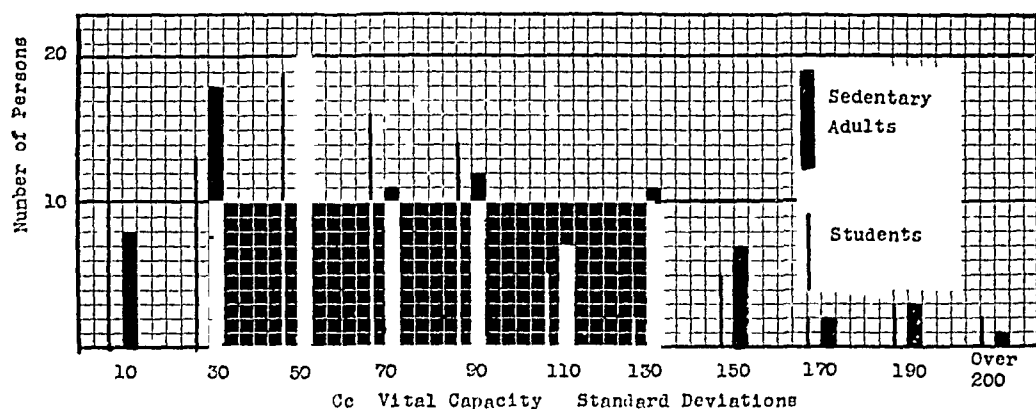
RESULTS

The results indicate that the vital capacity is not as useful a diagnostic procedure for the present group as for the students The chart shows clearly the greater deviations in vital capacity in the present group, and when analyzed statistically, the difference is found to be significant Interpreting it from the standpoint of usefulness in diagnosis, one could broadly state that in no case were the deviations from the "best straight line" of sufficient magnitude to interfere with the usefulness of the test in diagnosing pneumonia, but that for diseases exhibiting slight dimi-

2 Arnett, J. H., and De Orsay, R. H. *Am J M Sc* **193** 684 (May) 1937

nutions of vital capacity the test could be applied with confidence only to about half of the group. For example, if three times the standard deviation is taken as the criterion of significance and 250 cc as roughly representing the loss in vital capacity to be expected in early tuberculosis, determination of the vital capacity would be a reliable test for 54 of the present group, as compared with 68 of the young men of the previous study.

Further comparison of the present group with the younger men reveals that 63 of the older men exhibited losses in vital capacity, 11 remained the same and 26 gained, the average man losing 33.7 cc per year,³ the greatest annual loss being 250 cc and the greatest annual gain being 200 cc. Among the students only 12 lost, 72 gained and 16 remained the same, the average student gaining 66.9 cc per year, the greatest annual gain being 400 cc and the greatest loss 90 cc. These



Deviations in vital capacity from year to year. Deviations are expressed in terms of the standard deviation from the "best straight line" which could be drawn through the points representing all of the determinations of vital capacity.

figures are not surprising. Hutchinson, computing the average of single readings made on persons of different ages, concluded that after the age of 30 the vital capacity tends to diminish at the rate of 1.43 cubic inches (23.5 cc) per year.

CONCLUSIONS

The test of the vital capacity of the lungs is a useful diagnostic procedure, provided its potentialities and limitations are understood.

Its greatest field of usefulness is in groups subjected to periodic examinations.

The present study indicates that the test is more valuable for men of college age than for middle-aged men of sedentary occupation.

3 The figures given represent the slopes of the best straight lines, these being derived from the regression formula $Y = a + b(\bar{x} - \bar{y})$, see Fisher (Statistical Methods for Research Workers, ed 3, London, Oliver & Boyd, Ltd, 1930, pp 114-115).

EFFECT OF UREMIC SERUM AND URINE ON GROWTH OF FIBROBLASTS IN VITRO

M RACHMILEWITZ, M D

WITH THE ASSISTANCE OF MISS E NUSSBAUM

JERUSALEM, PALESTINE

Since the introduction of chemical analysis of blood in the investigation of renal disease and the use of tests of renal function, true uremia is considered as poisoning due to retention in the blood of urinary waste products. Almost every urinary constituent has been considered as the basic substance which causes the clinical symptoms displayed by patients with uremia. The attempt, however, to hold a single "uremia toxin" responsible for the clinical picture of uremia has failed. No single substance has been discovered the retention of which, as a result of renal insufficiency, produces uremia. The concept prevailing now (Volhard,¹ Fishberg² and Harrison and Mason³) has been clearly expressed by Fishberg: "Uremia is a complex autointoxication, the variegated clinical picture being the summation of the effects of retention of various urinary constituents." The most important substances which are considered as playing a role in the production of the uremic syndrome are the phenols, guanidine and urea. The mechanism of some of the clinical manifestations of uremia is ascribed also to disturbances of mineral metabolism. However, the possibility is not excluded that some, or possibly many, undefined substances are also concerned in the pathogenesis of uremia (Harrison and Mason³).

In view of the fact that the chemical analysis of body fluids and the investigation of the pharmacologic action of retained metabolites have not fully clarified the problem of uremia, old experiments concerning the toxicity of uremic blood and urine are still of interest. The methods

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From the Department of Experimental Pathology (Cancer Laboratories), the Hebrew University and Medical Department B of the Rothschild Hadassah University Hospital

1 Volhard, F, in von Bergmann, G, and Staehelin. Handbuch der inneren Medizin, ed 2, Berlin, Julius Springer, 1931, vol 6, pt 1, p 776

2 Fishberg, A M. Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1930

3 Harrison, T R and Mason, M F. The Pathogenesis of the Uremic Syndrome, Medicine **16** 1, 1937

used in the latter experiments consisted of injecting uremic blood or urine into animals and observing the effect. The first to carry out experiments of this kind was the French clinician Bouchard,⁴ in 1887. He found that normal human urine had a toxic effect on animals. Forty-five cubic centimeters of urine injected into the vein of a rabbit produced a lethal result. On the other hand, the urine of uremic patients was less toxic than that of normal persons.

The lesser toxicity of uremic urine was considered by Bouchard as evidence of retention in the blood of urinary toxins in uremia. Supplementary to these experiments were the subsequent ones of Roger⁵ and Herter.⁶ Roger injected blood serum of uremic patients into dogs and caused toxic manifestations similar to those of uremia. Herter made the same observations with blood serum obtained from dogs the ureters of which were ligated on both sides.

Serious objections were made to the method of demonstrating the toxicity of uremic serum and urine on experimental animals. The view has been expressed by investigators repeating these experiments (van den Bergh,⁷ Albu⁸ and Volhard¹) that the rate of injection was of greater significance for the result of the experiment than was the quantity of the injected serum or urine. The effect of foreign serum proteins might also lead to misinterpretation of the toxicity of uremic serum. In the experiments with urine injected into animals, great importance was assigned to the concentration of the urine and to the effect produced by the hypertonicity of the urine, which effect was wrongly interpreted by Bouchard and his pupils as being due to specific toxic properties of urine. Finally, the varying individual sensitivity of the experimental animal to the injected urine or blood was considered as one of the disadvantages of this method.

It seemed therefore justified to reinvestigate the problem of toxicity of uremic serum and urine by new methods. Tissue culture appeared to offer a suitable method for testing the general toxic nature of the materials concerned. Cell colonies growing in vitro form a convenient test object showing fundamental vital phenomena. The ingredients of the mediums which determine the growth of the cell colonies can

4 Bouchard, C. *Leçons sur les auto-intoxications dans les maladies*, Paris, F. Savv, 1887.

5 Roger, cited by Fishberg.²

6 Herter, C. A. *The Results of Experimental Nephrectomy in Dogs as Bearing upon the Uraemic State*, *M. Rec.* **52** 280, 1897.

7 van den Bergh, A. A. H. *Ueber die Giftigkeit des Harns*, *Ztschr. f. klin. Med.* **35** 53, 1898.

8 Albu, A. *Experimentelle Beiträge zur Lehre vom Harngift*, *Virchows Arch. f. path. Anat.* **166** 77, 1901.

be changed as required, and blood serums and urines to be examined can be added. The growth in the altered milieu can be measured and compared with control cultures, and the cell-toxic properties of the blood serums and urines to be examined can be deduced from the degree and nature of the effect of these substances on the development of the cell colonies.

EXPERIMENTAL METHODS

Uremic serum and urine were taken from patients suffering from severe renal insufficiency. In all cases, urea and uric acid were retained in the blood in varying degree and the usual clinical symptoms of uremia were present. Cases of uremia with complications, such as fever or icterus, were omitted from these series of experiments.

The pathologic serums and urines were tested on cultures of fibroblasts originating from chick embryo hearts. After three passages in hanging drops, the cultures were transferred to flasks and cultivated according to Carrel's standard method. The solid phase of the medium consisted of chick plasma diluted with Tyrode's solution, in the proportion 1:2, coagulated by 1 drop of diluted embryonic extract. To this was added as liquid phase the blood serum or sterile urine under examination. In experiments with uremic serum, the control flasks contained the same quantity of normal serum. In experiments with uremic urine, the control flasks contained the same quantity of Tyrode's solution or, in some cases, of normal urine.

In some of the experiments the effect of pathologic serums on cultures stimulated with embryonic extract was examined, the liquid phase in the test flasks consisting of embryonic extract and uremic serum, while to the control flasks embryonic extract and normal serum were added.

All experiments were carried out on sister cultures, one being used for the test experiment and the other for the control. The growth of the cultures was examined for a period of five to eight days, without change of the medium. The cultures were projected every day and were drawn and measured with a planimeter in accordance with Ebeling's method. The resulting values were used in plotting the growth curves.

INFLUENCE OF UREMIC SERUM ON GROWTH OF FIBROBLASTS IN VITRO

Behavior of Fibroblast Cultures in a Medium Containing Normal Human Serum—In a series of preliminary experiments the influence of normal human serum on the growth of chick fibroblasts in vitro was examined. Comparison was made between the growth of fibroblasts in flasks to which serum of healthy persons was added as liquid phase and that of fibroblasts in flasks to which Tyrode's solution was added. The experiments showed that the fibroblasts in mediums containing normal human serum developed regularly, during the period of observation of seven to eight days the increase in area of the cultures was constant (fig 1). The dimensions reached by the cultures at the end of this period ranged between 10 and 12 mm². These values corresponded to those reached by the cultures in the flasks with Tyrode's solution as liquid phase. Thus, the experiments showed neither a stimulating nor an inhibitory influence of the serum on the proliferation of cells. The appearance of the cultures in the flasks with serum

differed, however, from that of cultures growing in Tyrode's solution. The zone of growth of the latter appeared to be flat and the cultures were always transparent, while the serum cultures were more dense and compact, particularly in the central regions.

Behavior of Fibroblast Cultures in a Medium with Uremic Serum—EXPERIMENT 1. A 37 year old patient (Miz) was suffering from acute uremia, which appeared after a blood transfusion. At the time of the first observation, the urea content of the blood was 381 mg per hundred cubic centimeters.

The effect of the serum on cultures stimulated with embryonic extract was investigated. The liquid phase of the test flasks consisted of 0.5 cc of the patient's

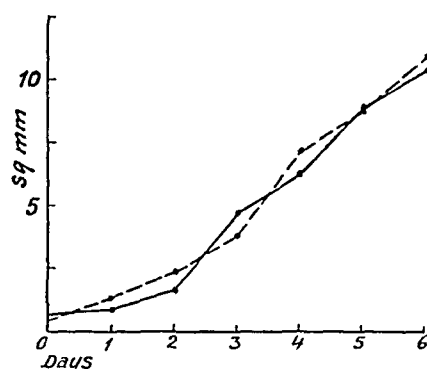


Fig 1—Growth curves of fibroblasts in normal serum (solid line) and in Tyrode's solution (broken line)

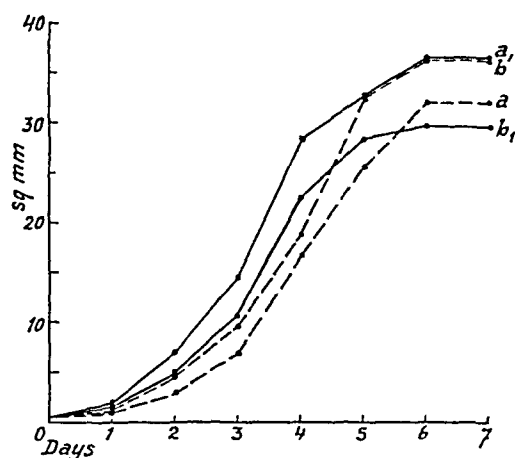


Fig 2 (patient Miz) —Growth curves of fibroblasts in uremic serum (solid line) and in normal serum (broken line) stimulated with embryonic extract. Sister cultures are designated by *a* and *a*₁ and *b* and *b*₁.

serum and 0.5 cc of a 15 per cent solution of embryonic extract. The control flasks contained embryonic extract of the same concentration, with the same quantity of normal human serum. The growth curves of both pairs of cultures are shown in figure 2.

A few days later, the urea content of the blood of the same patient was 414 mg per hundred cubic centimeters, and the experiment just described was repeated under identical conditions. The results are shown in figure 3.

Results The addition of uremic serum with a high urea content (381 and 414 mg per hundred cubic centimeters) had no injurious effect on the growth of the fibroblasts. The rate of growth was either the same or, as in the second part of the experiment, even slightly greater than normal. The appearance of the proliferating cells was entirely normal.

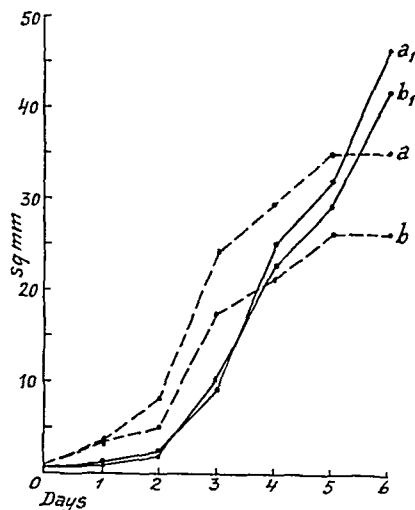


Fig 3 (patient M12) —Growth curves of fibroblasts in uremic serum (solid line) and in normal serum (broken line) stimulated with embryonic extract. Sister cultures are designated by *a* and *a*₁ and *b* and *b*₁.

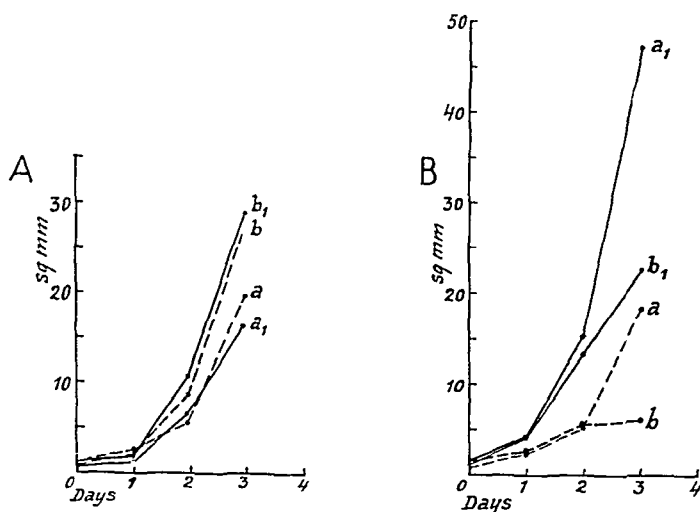


Fig 4 (patient Sh) —Growth curves of fibroblasts in uremic serum (solid line) and in normal serum (broken line) stimulated with embryonic extract. Sister cultures are designated by *a* and *a*₁ and *b* and *b*₁. *A* and *B* represent two sets of cultures.

EXPERIMENT 2 A 52 year old patient (Sh) was in a uremic state resulting from chronic nephritis. The content of urea in the blood was 272 mg per hundred cubic centimeters and that of uric acid 12.6 mg.

The effect of the serum of this patient on cultures stimulated with embryonic extract was examined. The liquid phase of the medium of the test flasks consisted of 0.5 cc of the patient's serum and 0.5 cc of a 15 per cent solution of embryonic extract. The control flasks contained embryonic extract of the same concentration and the same quantity of normal human serum. The growth curves of both pairs of cultures are shown in figure 4*A* and *B*.

Results The addition of uremic serum had no injurious effect on the growth of fibroblasts. Occasionally growth stimulation was observed. The appearance of the proliferating cells was entirely normal.

EXPERIMENT 3 A 52 year old patient (Sch) was suffering from arteriosclerotic, contracted kidney with uremia. The content of urea in the blood was 356 mg per hundred cubic centimeters and that of uric acid 11.2 mg.

The effect of the serum of this patient was tested on cultures stimulated with embryonic extract and on nonstimulated cultures. In the experiments on stimulated cultures the liquid phase of the medium of the test flasks consisted of 0.5 cc

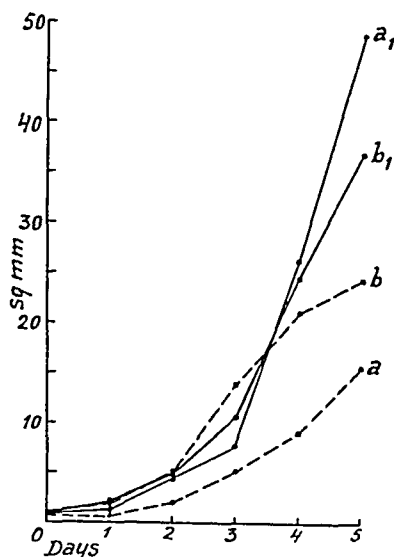


Fig 5 (patient Sch) —Growth curves of fibroblasts in uremic serum (solid line) and in normal serum (broken line) stimulated with embryonic extract. Sister cultures are designated by *a* and *a*₁ and *b* and *b*₁.

of the patient's serum and 0.5 cc of a 15 per cent solution of embryonic extract. The control flasks contained embryonic extract of the same concentration and the same quantity of normal human serum. The growth curves are shown in figure 5. In the experiments without addition of embryonic extract the liquid phase of the medium of the test flasks consisted of 1 cc of the patient's serum, while the control flasks contained 1 cc of normal human serum. The growth curves of these cultures are shown in figure 6*A*, *B* and *C*.

Results The cultures with or without embryonic extract grew with the addition of uremic serum better than those with normal serum. The proliferating cells had an entirely normal appearance.

EXPERIMENT 4 A 68 year old man (F) was suffering from uremia of unknown cause. The content of urea in his blood was 380 mg per hundred cubic centimeters.

The effect of the serum of this patient on cultures stimulated with embryonic extract and on nonstimulated cultures was tested. In the experiments on stimulated

cultures the liquid phase of the medium of the test flasks consisted of 0.5 cc of the patient's serum and 0.5 cc of a 15 per cent solution of embryonic extract. The control flasks contained embryonic extract of the same concentration and the

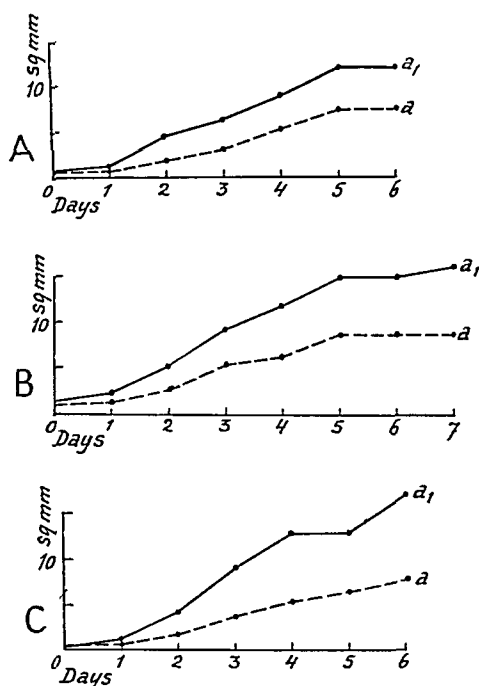


Fig 6 (patient Sch) —Growth curves of fibroblasts in uremic serum (solid line) and in normal serum (broken line) Sister cultures are designated by a and a_1 and b and b_1 . A, B and C represent three sets of cultures

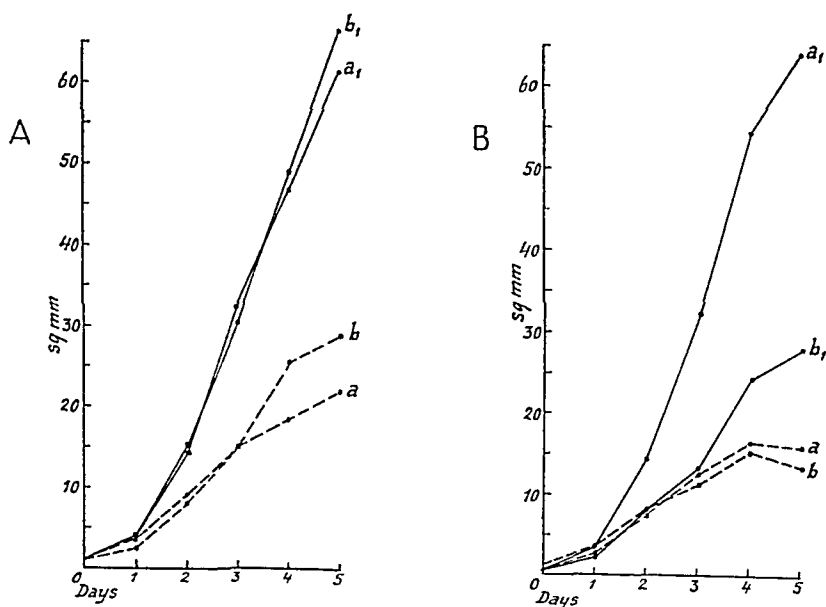


Fig 7 (patient F) —Growth curves of fibroblasts in uremic serum (solid line) and in normal serum (broken line) stimulated with embryonic extract. Sister cultures are designated by a and a_1 and b and b_1 . A and B represent two sets of cultures

same quantity of normal human serum. The growth curves are shown in figure 7 *A* and *B*. In the experiments on nonstimulated cultures the liquid phase of the medium of the test flasks consisted of 1 cc of the patient's serum, while the control flasks contained 1 cc of normal human serum. The growth curves of these cultures are shown in figure 8.

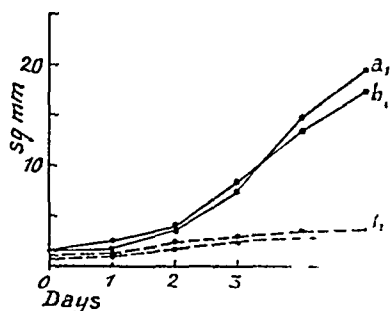


Fig 8 (patient F) —Growth curves of fibroblasts in uremic serum (solid line) and in normal serum (broken line). Sister cultures are designated by a and a_1 and b and b_1 .

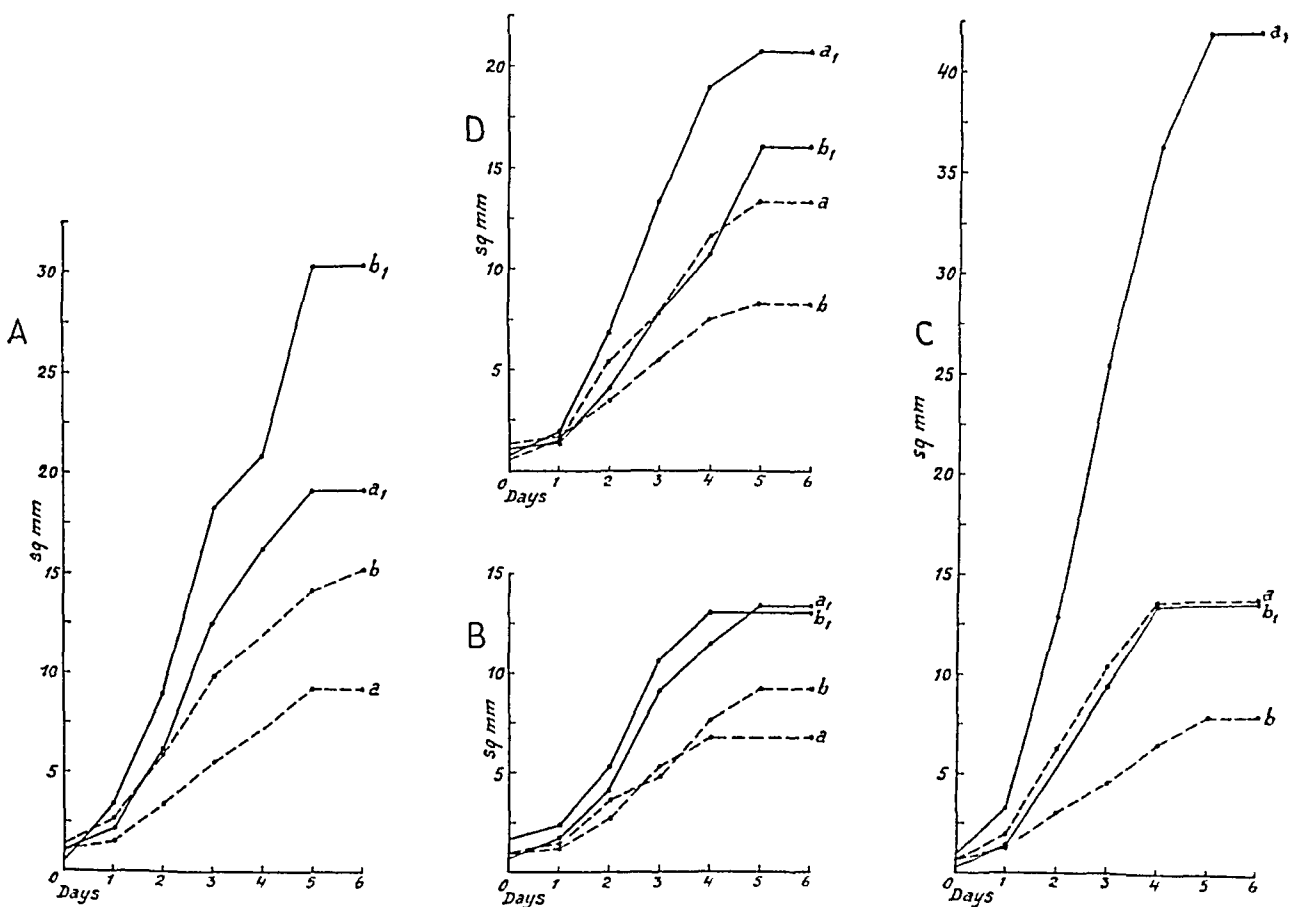


Fig 9 (patient R Sh) —Growth curves of fibroblasts in uremic serum (solid line) and in normal serum (broken line). Sister cultures are designated by a and a_1 and b and b_1 . *A*, *B*, *C* and *D* represent four sets of cultures.

Results In all experiments, with or without addition of embryonic extract the uremic serum had a stimulating effect on growth. The proliferating cells had an entirely normal appearance.

EXPERIMENT 5 A 43 year old woman (R Sh) was suffering from severe renal insufficiency caused by chronic nephritis. The content of urea in the blood at the time of the experiment was 245 mg per hundred cubic centimeters.

The effect of the serum of this patient was tested on nonstimulated cultures. The liquid phase of the medium of the test flasks consisted of 1 cc of the patient's serum, while the control flasks contained 1 cc of normal human serum. The growth curves of the cultures are shown in figure 9A, B, C and D.

Results The addition of the uremic serum in this case resulted in considerable stimulation of growth in all experiments. The proliferating cells had an entirely normal appearance.

In summary of the results of the experiments with uremic serum, it may be concluded that uremic serum added to cultures of fibroblasts had no injurious effect on the cells or inhibitory influence on the growth of the cultures. Moreover, it may have had a certain stimulating effect on cell proliferation.

EFFECT OF UREMIC URINE ON GROWTH OF FIBROBLASTS IN VITRO

It was shown in a previous report⁹ that normal human urine added to cultures of fibroblasts has a definite injurious effect on growth. The addition of higher concentrations of urine (1 and 0.5 cc, specific gravity, 1.026 to 1.030) to the usual contents of the flask causes complete inhibition of cell proliferation. Smaller concentrations of urine inhibit the growth rate of the cell colonies, the degree of inhibition being parallel to the concentration of urine. When 0.25 cc of urine was added a barely perceptible growth was observed. After the addition of 0.1 cc there was appreciable growth, but distinctly less than in the controls. The inhibition of growth was also generally noticeable with 0.05 cc of urine. The method of demonstrating the toxicity of urine by its effect on the growth rate of colonies of fibroblasts has proved exceedingly sensitive and provided a quantitative method for measuring urinary toxicity.

This method was used in the following experiments to determine the toxicity of uremic urine.

The urines of 4 uremic patients were tested in this manner.

EXPERIMENT 1 A 52 year old patient (S H) was in a uremic state from arteriosclerotic, contracted kidney. The content of urea in the blood was 272 mg per hundred cubic centimeters. The maximum specific gravity of the urine was 1.006.

Urine of this specific gravity was added to the test flasks as the liquid phase of the medium. The growth of cultures in these flasks was compared with the growth of their sister cultures in the control flasks, containing Tyrode's solution as the liquid phase of the medium.

⁹ Rachmilewitz, M. Toxic Effect of Human Urine on Fibroblasts Growing in Vitro, *Proc Soc Exper Biol & Med* **43** 497, 1940.

Results After the addition of 1 cc of urine only slight growth was observed. A noticeable inhibition of growth was also seen when 0.5 cc of urine was added.

EXPERIMENT 2 A 50 year old patient (R) had a clinical diagnosis of malignant hypertension with uremia. The content of urea in the blood was 195 mg per hundred cubic centimeters. The maximum specific gravity of the urine was 1.014. The experiment was carried out under the same conditions as the preceding one.

Results There was no growth either with 1 cc or with 0.5 cc of urine.

EXPERIMENT 3 A 43 year old patient (R. S.) had a clinical diagnosis of chronic nephritis with uremia. The content of urea in the blood was 102 mg per hundred cubic centimeters. The maximum specific gravity of the urine was 1.010. The experimental conditions were those of experiments 1 and 2 in this group.

Results There was a complete inhibition of growth with the addition of 1 cc of urine. The occurrence of single cells or considerable inhibition of growth was observed with 0.5 cc of urine. Distinct inhibition of growth was noticed with 0.25 cc of urine.

EXPERIMENT 4 A 26 year old patient (V. M.) had a clinical diagnosis of chronic nephritis and preuremia. The content of urea in the blood was 56 mg per hundred cubic centimeters. The maximum specific gravity of the urine was 1.010. The experimental conditions were those of experiments 1 and 2 of this group.

Results Complete inhibition of growth was observed with the addition of 1 cc of urine.

EXPERIMENT 5 In another experiment the urine of the patient just mentioned (V. M.) was tested against normal urine of the same specific gravity (1.010).

Results When 1 cc of urine was added there was complete inhibition of growth of the test cultures as well as of the control cultures. With 0.5 cc of urine there was extreme inhibition of growth, and with 0.25 cc, less but definite inhibition of growth of both the test and the control culture.

The experiments have thus shown that the uremic urine, though of low specific gravity, has an extremely injurious and inhibitory effect on fibroblasts growing in vitro.

Uremic urine showed the same degree of toxicity as normal urine of the same concentration.

COMMENT

The fact which I previously demonstrated, that normal human urine contains substances which have a toxic effect on cells in vitro, raised the problem whether these cell-damaging substances are retained in the blood of uremic patients, and, thus, may have a bearing on the symptom complex of uremia. The examination of this possibility was carried out in the reported experiments.

Investigation was made to determine two things: (1) whether the cell-damaging effect of uremic urine was lessened through the retention of the toxic substances concerned and (2) whether the retention of these substances resulted in their accumulation in the blood.

The experiments have shown that the cell-toxic effect of uremic urine does not differ from that of normal urine and that these cell-toxic substances could not be demonstrated in uremic blood in effective concentrations. The two observations are in accord.

Results obtained on a definite test object, in this instance the cell culture obviously cannot be related without reservation to the complicated mechanism of the entire human body. With such reservation in mind, it can be stated in any case that the urinary substances which are definitely toxic for the cell *in vitro* are not retained in uremic blood, at least not in effective concentrations.

The lack of toxic effect of uremic serum on cells cultivated *in vitro* is not surprising in the light of the modern concept of the pathogenesis of uremia. The variability of the clinical symptoms of uremia alone speaks against the assumption that the uremic symptom complex can be related to accumulation in the blood of a single toxic substance. Various factors are considered responsible for the production of the clinical picture of uremia. Even Volhard, who stressed the significance of retained phenols for the causation of uremic symptoms, assumed that the clinical picture of uremia could be more fully explained by indirect toxic action than by the direct effect of one particular poison. The muscular irritability occasionally observed in patients suffering from uremia may serve as an example of indirect toxic effect caused by the lowering of the calcium content of the blood secondary to retention of phosphates. Likewise, urea, a substance of relatively low toxicity, may be indirectly toxic in at least two ways. 1 Urea may increase penetration into the body cells of potentially toxic substances (Baur ¹⁰). 2 Together with other retained excretory products, urea may interfere with detoxifying mechanisms of the body, leading to accumulation of substances which normally occur only in traces (Fishberg). Thus, Mason and his co-workers have shown that previous injections of urea in dogs caused a definite delay in disappearance from the blood stream of administered guanidine.

It is thus possible that in the production of uremic symptoms an important role can be ascribed to the accumulation of toxic substances in the tissues and to disturbances of cellular activity of various organs rather than to toxins circulating in the blood.

Another evidence of the low toxicity of uremic blood has been given by Russian workers, who have used uremic blood for transfusion in human beings and in animals (Veselkin and Kapica ¹¹). They could not

10 Baur, M. Zur Pharmakologie des Harnstoffs (Beiträge zum Problem der Uramie), *Arch f exper Path* **167** 104, 1932.

11 Veselkin, P. N., and Kapica, L. M. Experimental Observations Concerning Transfusion of Uremic Blood, *Vestnik chir* **48** 9, 1936.

observe any untoward effects of the uremic blood. Moreover, because of its effect on the coagulation of blood, they have recommended its use to stop bleeding in hemorrhagic conditions.

The last point to be discussed is the stimulating effect of uremic serum on the growth rate of the fibroblast cultures observed in some of the experiments. Since Carrel's classic studies concerning the growth-promoting factors in tissue culture, it is known that intermediary protein metabolites (proteoses) stimulate cell multiplication. Recently it has been found that allantoin, a derivative of purine, stimulates the healing process of deep purulent wounds. Urea was found to be even more effective than allantoin. Since urea may be obtained from allantoin by hydrolysis, Hetherington and Shipp¹² expressed the opinion that the growth-promoting effect of allantoin might be due to the urea and not to allantoin itself. However, while they could demonstrate the stimulating effect on fibroblast cultures when allantoin was added to the medium, they failed to observe the same effect with urea.

The available evidence does not permit a conclusive definition of the substance in the uremic serum which is responsible for the stimulation of growth, but it is well justified to assume that this effect is caused by retained products of intermediary protein metabolism.

SUMMARY

Fibroblast colonies were used as the test object to examine the toxicity of uremic serum and urine. The experiments have shown that uremic serum added to the medium has no injurious or inhibitory effect on the growth of fibroblasts. Stimulation of growth was observed with some uremic serums with a high content of urea as compared with that of normal serums. Urine from uremic patients interferes with growth of fibroblasts *in vitro* as does normal urine. The significance of these experiments in relation to the problem of uremia is discussed.

¹² Hetherington, D. C., and Shipp, M. E. Effect of Urea upon Growth of Fibroblasts from Cardiac Explants in Tissue Culture. *Proc. Soc. Exper. Biol. & Med.* **37**: 238, 1937.

INFARCTION OF THE LUNG

A CLINICAL AND ROENTGENOLOGIC STUDY

GEORGE R KRAUSE, M D

AND

EDWARD M CHESTER, M D

CLEVELAND

The clinical recognition of pulmonary infarction in many instances is difficult. This is illustrated by the fact that in only 22 per cent of our cases was the condition diagnosed correctly ante mortem. This study was made in an attempt to correlate the clinical and roentgenologic data with the pathologic observations and thus improve our diagnostic accuracy.

From Jan 1, 1930 to Dec 31, 1939 6,548 autopsies were performed at Cleveland City Hospital. Among these were found 344 instances of aseptic hemorrhagic infarction of the lung, an incidence of 5.2 per cent. In 174 of these 344 cases the infarct was considered to be the major cause of death or an important contributory factor. The infarct was considered significant if it was 5 cm in size or larger. Multiple infarcts, even if smaller, were considered significant. However, even if it was large, the infarct was classified as unimportant if another adequate cause of death existed, for example, generalized peritonitis or carcinomatosis. In addition, an infarct, regardless of its size, was considered significant if its onset coincided with a definite change for the worse in the course of the patient's illness. On the basis of these criteria, pulmonary infarct was found to be a significant cause of death in 174 instances, or 2.7 per cent of our postmortem material.

Belt,¹ studying a series of 1,990 consecutive autopsies, found 155 instances of hemorrhagic infarct of the lung, excluding cases of septicemia, an incidence of 7.8 per cent. Hampton and Castleman,² in 3,500 autopsies at Massachusetts General Hospital, found pulmonary embolism or infarction in 315 cases, or 9 per cent.

From the Departments of Roentgenology and Medicine of Cleveland City Hospital and Western Reserve University School of Medicine.

1 Belt, T H. The Aetiology of Lung Infarction, Brit Heart J **1** 283-289 (Oct) 1939.

2 Hampton, A O, and Castleman, B. Correlation of Postmortem Chest Teleoroentgenograms with Autopsy Findings, Am J Roentgenol **43** 305-326 (March) 1940.

SOURCE OF THE THROMBUS IN THE PULMONARY ARTERY

An attempt was made to determine the origin of the thrombus in the pulmonary artery from a study of the clinical records and autopsy protocols. This was not successful, since in 54 per cent of the cases no source could be found. One cannot infer that in these cases the thrombus originated in the pulmonary artery, although in many of them it may have done so. In the majority of instances the extremities were not examined, and in other cases the protocols were not complete. Belt¹ and Gsell² stated that in most of the cases they reported the infarct was embolic in origin. However, Roubier³ expressed the belief that infarction most frequently followed local thrombosis, presumably because of slowing of the circulation. This opinion may be due to the fact that the underlying cause of death in all of the cases he reported was heart disease.

SITE OF THE INFARCT

Many authors have noted that the lower lobe, especially of the right lung, is the most frequent site of infarction. Such a distribution was also found in our material. The lower lobe of the right lung was the only lobe involved in 27 per cent of the cases, and the lower lobe of the left lung in 15 per cent. However, the lower lobe of the right lung alone or in combination with other lobes was the site of an infarct in 69 per cent of the cases, and the lower lobe of the left lung alone or with other lobes, in 53 per cent. The remaining lobes were rarely involved alone.

INFARCT AND HEART DISEASE

In Hosoi's⁴ group of 25 cases of postoperative embolism, in 12 of which pulmonary infarction occurred, it was noted that a large heart was present in 9. In the 1,990 cases with autopsy analyzed by Belt,¹ there were 235 instances of death from heart disease. In 70 of these cases pulmonary infarction was present. In 52, gross cardiac failure antedated the infarct.

Levine and White⁵ found 22 instances of pulmonary infarction in 62 cases of hypertensive and rheumatic heart disease in which gross

3 Gsell, O. Hemorrhagic Pulmonary Infarction and Its Complications, *Deutsche med Wchnschr* **61** 1317-1320 (Aug 16) 1935

4 Roubier, C. Comparative Frequency and Pathogenesis of Pulmonary Infarcts in Different Cardiopathies, *Lyon med* **162** 181-189 (Feb 12) 1939

5 Hosoi, K. Pulmonary Embolism and Infarction, *Ann Surg* **95** 67-72 (Jan) 1932

6 Levine, H. B., and White, P. D. Pulmonary Infarction Complicating Severe Diseases of the Mitral Valve, *Arch Int Med* **60** 39-50 (July) 1937

cardiac failure occurred. In a parallel group of 72 cases in which there was no cardiac failure there were only 7 cases of infarct.

McCartney⁷ stated that the incidence of pulmonary infarction, occurring postoperatively, doubled when heart disease was present.

Of 241 cases in our material in which there was heart disease and pulmonary infarction, irrespective of the presence of cardiac failure, the infarct was an important cause of death in 157, or 65 per cent. Of 103 cases in which there was no heart disease, the infarct was significant in only 17, or 16 per cent (table 1). The latter group included 21 cases of postoperative infarction, in only 5 of which the infarct was large.

PLEURAL EFFUSION

Gsell³ noted the presence of a pleural effusion in one half of his patients who had a pulmonary infarct. He cited Krehl's statement that

TABLE 1—*Incidence of Infarction and Cardiac Disease in Three Hundred and Forty-Four Cases*

Cases of cardiac disease and pulmonary infarct	241		
Infarct significant as a cause of death		157	65%
Infarct only incidental		84	35%
Cases of infarct without cardiac disease	103		
Infarct significant as a cause of death		17	16%
Infarct only incidental		86	84%
		<hr/> 344	

an obstinate, seemingly primary, serous pleural effusion in a patient with heart disease is often due to infarct. In this respect the data from our material was difficult to evaluate. In a large number of cases there was pleural effusion, but in many there was also cardiac failure. From a study of the charts alone it was often impossible to determine whether the infarct preceded the fluid. However, there were a number of instances in which this sequence was definite, and in a few instances hydrothorax developed without evidence of heart disease.

In most cases the effusion was serous, although in some it was serosanguineous. In others the notation was made that bile pigments were present. The presence of such substances in pleural effusion due solely to cardiac failure is unusual, since the fluid is a pure transudate and should not contain bile pigments.

⁷ McCartney, J. S., cited by Barnes, A. R. Pulmonary Embolism, J. A. M. A. 109:1347-1353 (Oct. 27) 1937.

CLINICAL OBSERVATIONS

In 73 of the 174 cases in which the infarct was a significant cause of death, the clinical observations could be correlated with those made at postmortem examination. These data are summarized in table 2. Hemoptysis, often repeated, with the blood usually bright red and of small amount, was the most frequently noted symptom. Pain and an increase in dyspnea were next in frequency. The usual physical signs were those of consolidation and pleural effusion. Pleural friction rubs were occasionally heard.

Bullowa⁸ and Lord and Hefron⁹ stated that a chill might occur in association with pulmonary infarction, but the latter authors stated the opinion that it was less common than in lobar pneumonia. Gsell³ found an initial chill to be present in only 1 per cent of his 200 cases. The latter observation is in accord with our experience since in none of the 73 cases was a history of a chill elicited.

TABLE 2—Occurrence of Signs and Symptoms in Seventy-Three Cases

Hemoptysis	48	65%
Rales	48	65%
Pain	25	32%
Dulness	25	31%
Dyspnea (increase in)	22	30%
Bronchial breath sounds	15	20%
Friction rub	9	12%
Cough, no hemoptysis	5	7%

In 55 of these 73 cases there was clinical evidence that the infarct had occurred within the last twelve days of life. In 23 cases the infarct was followed by death in three days or less. The approximate age of the infarct was consistent with the history in all 73 cases. This short interval between the occurrence of a pulmonary infarct and death indicates that this complication carries a grave prognosis.

On the same day that the infarct made itself evident there was an average increase in the temperature of 1.5 C (2.7 F). The pulse rate increased 20 beats per minute and the respiratory rate 8 per minute.

Icterus, which is usually considered a common accompaniment to pulmonary infarction, was noted in some cases. Its occurrence however, was not sufficiently frequent to permit evaluation of its significance, especially since another possible cause of icterus was often present namely severe passive hyperemia of the liver.

8 Bullowa J. C. *The Management of the Pneumoniae*, New York: Oxford University Press, 1937.

9 Lord F. T. and Hefron, R. *Pneumonia and Serum Therapy*. New York: The Commonwealth Fund, 1938.

There were several cases in this series in which a secondary abscess developed in the infarct, with a bronchopleural fistula and empyema. In this group expectoration of foul purulent sputum was present. This interesting group is being studied in detail and will be reported later.

ROENTGENOLOGIC OBSERVATIONS

A number of authors, including Kirklin and Faust,¹⁰ Levy,¹¹ Jellen,¹² Westermarck,¹³ Smith¹⁴ and Hampton and Castleman,² have discussed the roentgenologic findings in pulmonary infarction. All stressed the varied appearance of the infarcts, depending on their size, position and age and the presence of secondary infection, passive hyperemia or pleural effusion. In general, it has been noted that the typical post-mortem appearance of a triangular infarct, situated in a lower lobe, is the exception rather than the rule in the roentgenogram, unless exposures are made in more than one projection. This variation in the shadow is due to the fact that unless the roentgen rays pass at right angles to the infarct, the shadow will be ovoid, rather than triangular. If they pass through the infarct in its long axis, the shadow will be round. The finding of a round shadow has been responsible for at least one attempted pneumonectomy for supposed tumor of the lung.¹⁵

The density of the shadow is usually less than that seen in lobar pneumonia, since less of the lung is involved. The shadow will change little in twenty-four hours, whereas in the early stages of lobar pneumonia the shadow may show an extensive spread.

At times the appearance is only that of a hazy horizontal streaking at the base, usually with some elevation of the diaphragm. This streaking may simulate localized patches of atelectasis. The hilar shadows are usually accentuated, although the passive hyperemia which is often present may account for this appearance. However, Westermarck¹³ made the

10 Kirklin, B. R., and Faust, F. S. A Clinical and Roentgenologic Consideration of Pulmonary Infarction, *Am J Roentgenol* **23** 265-275 (March) 1930.

11 Levy, H. Atypical Roentgen Appearance of Pulmonary Infarction in Patients with Heart Failure, *Am J Roentgenol* **35** 635-639 (May) 1936.

12 Jellen, J. The Roentgenological Manifestation of Pulmonary Embolism with Infarction of the Lung, *Am J Roentgenol* **41** 901-908 (June) 1939.

13 Westermarck, N. On Roentgen Diagnosis of Lung Embolism, *Acta radiol* **19** 357-372, 1938.

14 Smith, K. S. The Radiology of Pulmonary Infarction, *Quart J Med* **7** 85-99 (Jan) 1938.

15 Coste, F., and Bolgert, M. Round Roentgen Image Due to White Infarction Resulting from Endarteritis, *Bull et mem Soc med d hôp de Paris* **57** 1362-1368 (Nov 27) 1933.

interesting observation that if roentgenograms were made within an hour or two of the occlusion of the branch of the pulmonary artery, an area of avascularity in the pulmonary field was noted. This same area later showed an increase in density, due to the infarct which followed.

Secondary bronchopneumonia may occur, causing edges of the shadow to appear feathery, rather than well defined. The development of a pleural effusion may obscure the infarct entirely. Secondary abscess formation, with or without the development of a bronchopleural fistula and empyema, may occur. This complication will further obscure the picture, particularly if the patient is not seen until the late stages of his illness.

Even a small infarct may leave a shadow which persists for many months, or even years. The residual shadow resembles streaks of fibrous tissue. Such a shadow has been noted in some of our cases (not included in the statistical series) in which the patients have recovered.

The shadow of an infarct must be differentiated from that seen in cases of lobar pneumonia, bronchopneumonia, abscess, neoplasm, cyst, passive hyperemia and interlobar effusion.

Examples of the different types of shadows and brief case histories are included in this report.

DIAGNOSIS

While the difficulties interposed by the presence of cardiac failure are recognized, it is evident that the diagnosis of infarction will be made only as often as the condition is thought of and looked for clinically. The classic symptoms of hemoptysis, thoracic pain, dyspnea and fever and the physical signs indicating involvement of the lung and the overlying pleura should point to such a diagnosis. In addition, the presence of a persistent pleural effusion, especially if bile pigments are present, in a patient with cardiac failure, together with an otherwise unexplained fever should suggest the diagnosis of an infarct underlying the effusion, even if the classic symptoms are absent. That unexplained fever may often be due to an infarct was mentioned by Kinsey and White,¹⁶ who studied the occurrence of fever in cases of congestive heart failure. They found pulmonary infarction present in 24 out of 50 cases in which autopsy was performed. All of the patients had had an unexplained fever during their stay in the hospital.

The appearance of the roentgenograms may be of great help if they are taken before a pleural effusion obscures the pulmonary fields and

16 Kinsey, D., and White, P. D. Fever in Congestive Heart Failure, *Arch Int Med* **65** 163-170 (Jan.) 1940.

if the varied appearance of the infarcts is borne in mind. Roentgenograms taken in more than one projection will often clarify the problem.

However, of our series of 174 cases of significant pulmonary infarct, in only 22 per cent was the condition correctly diagnosed clinically. In 28 per cent it was called bronchopneumonia. In 50 per cent no diagnosis of any pulmonary lesion other than passive hyperemia was made. Roubier⁴ and others have reported similar experiences.

Clinically, pulmonary infarct must be differentiated from pneumonia. The presence of bacteria, especially pneumococci, in the sputum or blood and a prompt response to specific serum therapy or chemotherapy would favor the diagnosis of pneumonia. The absence of a chill, the rapid accumulation of a pleural effusion and an increase in the signs of cardiac failure would point to the presence of an infarct.

Right hydrothorax is a frequent occurrence in cases of cardiac failure. The fact that infarction of the lung occurs so much more frequently on the right side and by itself can cause a pleural effusion may in part explain this well known observation.

REPORT OF FIVE CASES

CASE 1—F. B., a white man aged 28, known to have rheumatic heart disease with mitral stenosis, was admitted to the medical service on Feb. 11, 1940 in a condition of moderately severe cardiac failure. The course of his illness was satisfactory until the twenty-eighth day of hospitalization, when he expectorated a small amount of blood. On the thirty-second day he again had hemoptysis, together with a pleuritic pain on the right side. Two days later, after the removal of 400 cc. of serosanguineous fluid from the right pleural space, a roentgenogram revealed an ovoid area of increased density in the upper lobe of the right lung (fig. 1A). The next day an examination with the patient in the second oblique position showed the shadow to be slightly more dense, well defined, triangular and anterolateral in position, just above the interlobar septum (fig. 1B).

Small daily hemoptyses continued. On the fortieth day the patient's sputum was found to be purulent and foul, and examination revealed right pneumothorax. The latter observation was confirmed by a roentgenogram, which also revealed a fluid level in the pleural space, an area of diminished density in the upper lobe of the right lung and a dense shadow opposite the left hilus. The last was thought to represent another infarct (fig. 2). The patient died that evening, twelve days after his first hemoptysis.

Autopsy revealed rheumatic heart disease with mitral stenosis, mural thrombi in the right atrium and emboli in several branches of the pulmonary artery. In the upper lobe of the right lung was a moderately fresh infarct in the position indicated by the roentgenograms, with necrosis in the center, a bronchopleural fistula and a seropurulent effusion (fig. 3). In the lower lobe of the right lung there were two large infarcts, with abscess formation but without communication with the pleural space. There was a large fresh infarct in the upper lobe of the left lung.

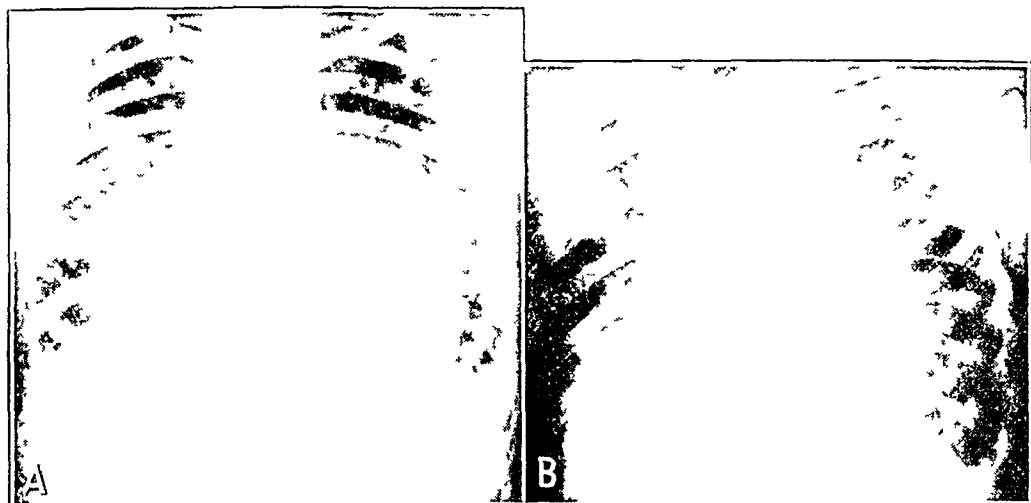


Fig 1 (case 1)—*A*, roentgenogram taken March 21, 1940. The cardiac shadow is enlarged and has a straight-line border. The increased density of the hilar markings indicates the presence of passive hyperemia. Just above the interlobar septum on the right side there is a sharply demarcated ovoid shadow, which represents the infarct in the upper lobe of the right lung. *B*, roentgenogram made March 22, with the patient in the second oblique position. The shadow is triangular and lies anteriorly in the upper lobe of the right lung at the interlobar septum.

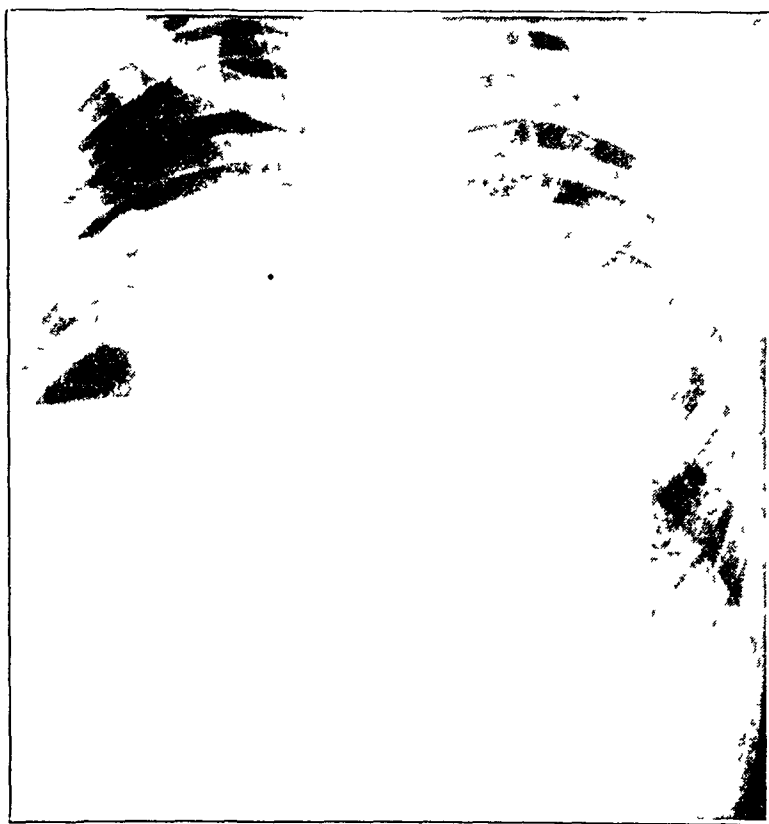


Fig 2 (case 1)—Roentgenogram taken March 26, 1940. Pneumothorax is present on the right, with a pleural effusion and some adhesion bands. Apparent "honeycombing" in the collapsed upper lobe of the right lung indicated probable formation of an abscess. There is a dense shadow, which proved to be an infarct, opposite the lower portion of the left hilus.

This case illustrates the variation in the appearance of the shadow of the infarct in different projections and also the development of a bronchopleural fistula with empyema, obscuring the infarct entirely

CASE 2—J Z, a white man aged 70, was admitted to the surgical service on March 13, 1939 for a lumbar sympathectomy, because of peripheral vascular disease. On the fifth day after operation, pain developed in the left upper quadrant of the abdomen and the patient had a small hemoptysis. A roentgenogram (fig 4A) taken the next day showed streaked shadows in the lower lateral

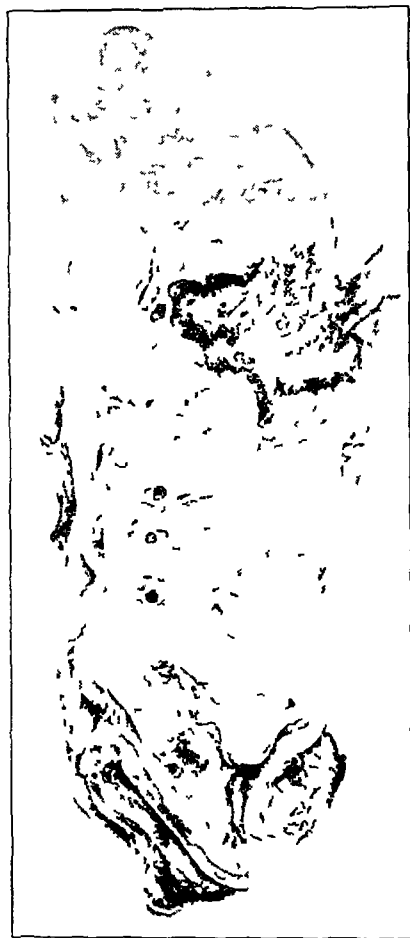


Fig 3 (case 1)—A section through the fixed right lung shows the infarct, with necrosis in the center. The arrow points to the communication between the abscess and the pleural space.

portion of the left pulmonary field, the whole streaked area being ovoid. Four days later a lateral view of the chest (fig 4B) showed the infarct to be situated posteriorly in the lower lobe of the left lung and to be triangular. The patient died on the twelfth day after operation, seven days after the infarct occurred.

Postmortem examination confirmed the diagnosis of an infarct in the lower lobe of the left lung and revealed the lesion to be 5 cm in length. Several more recent, smaller infarcts were also present.

This case illustrates that the triangular shape of the infarct may be revealed in projections other than the conventional posteroanterior one.

CASE 3—D W, a woman aged 57, was admitted in a moribund state to the medical service on March 23, 1939. Physical examination revealed consolidation of the lower lobe of the right lung, thrombophlebitis in the region of the right ankle and cellulitis of the right forearm. A roentgenogram (fig 5) revealed a few streaks of increased density, horizontal in position, just above the right half of the diaphragm, which was elevated. These streaks suggested localized patches of atelectasis. A diagnosis of septicemia was made and sulfanilamide was administered, but the patient died twenty-six hours after admission.

Autopsy revealed acute bacterial endocarditis, due to *Streptococcus haemolyticus*, and recent infarcts of the lower lobe of the right lung, just above the diaphragm.

In spite of the fact that the roentgenogram in this case was taken within a few hours of death and that well defined infarcts were found at autopsy, the roentgenogram revealed only a few horizontal streaks of increased density, suggesting localized plaques of atelectasis.

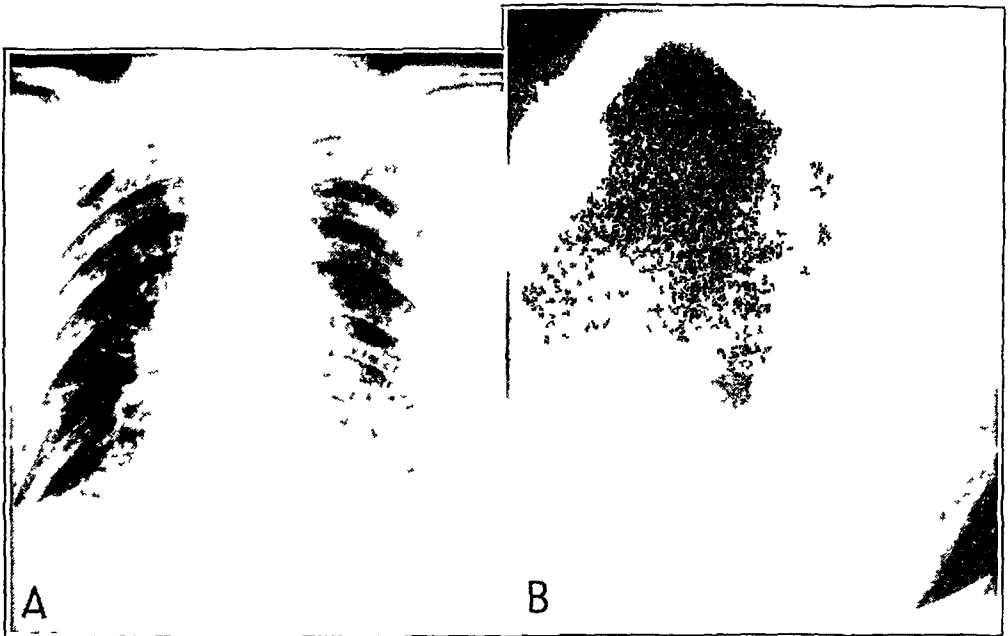


Fig 4 (case 2)—*A*, an ovoid area of increased density, streaked in appearance, in the lower lateral portion of the left pulmonary field. The left half of the diaphragm is elevated. Considerable emphysema is present. *B*, left lateral view of the chest as seen in a roentgenogram taken four days after that shown in figure 4 *A*. A definitely triangular area of increased density is located posteriorly in the lower lobe of the left lung.

CASE 4—A J, a white girl aged 16, was admitted to the medical service on May 5, 1939, with the diagnosis of rheumatic pancarditis. Four days before admission she had had a small hemoptysis and some pain in the right side of the chest. Both recurred daily until the third day of hospitalization, at which time a roentgenogram (fig 6) of the chest revealed an enlarged cardiac shadow, with a mitral configuration. Great accentuation of the hilar shadows indicated the presence of severe passive hyperemia. No infarcts were seen.

The patient died May 19, the fourteenth day of hospitalization, and post-mortem examination revealed a large organizing infarct in the lower lobe of

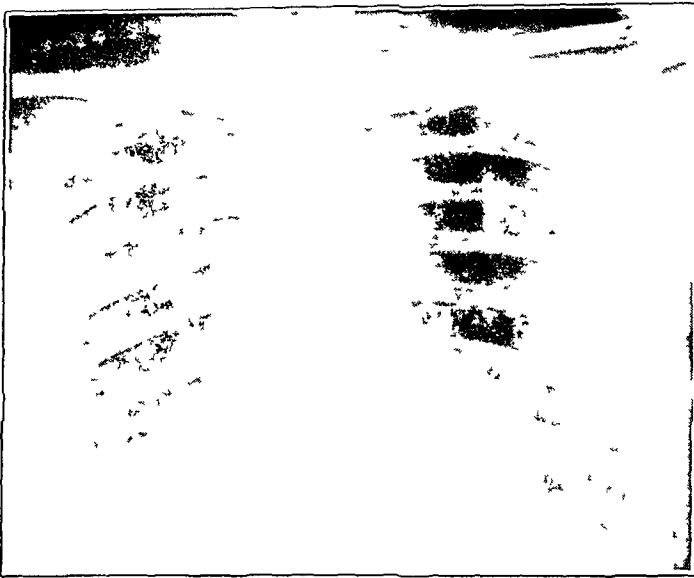


Fig 5 (case 3)—An anteroposterior view of the chest, as seen in a roentgenogram taken with the patient recumbent, shows a few streaks of increased density parallel to and just above the right half of the diaphragm. At autopsy a few hours later, a fresh but well demarcated infarct was present in this location.

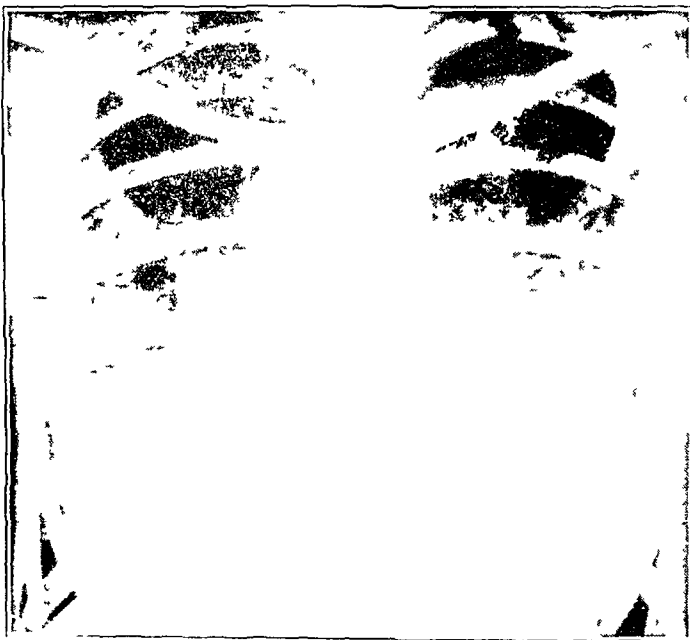


Fig 6 (case 4)—The cardiac shadow is seen to be enlarged, and the left cardiac border is convex. A large amount of passive hyperemia is present, as evidenced by an increase in density of the hilar shadows. Although definite infarcts were present in the right lung at autopsy and were undoubtedly present at the time this roentgenogram was made, a diagnosis cannot be made.

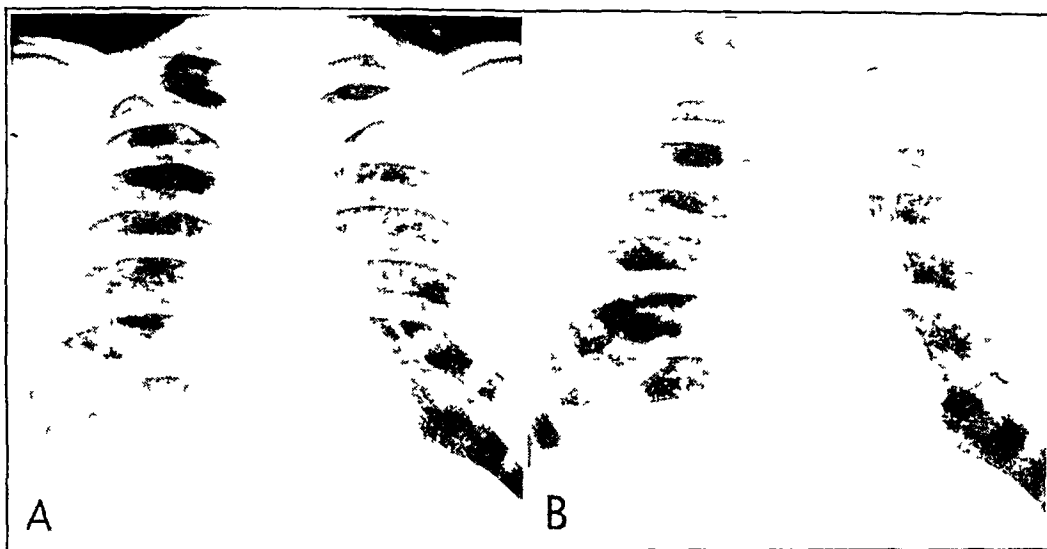


Fig 7 (case 5)—*A*, posteroanterior view of the chest in a roentgenogram made on the day of admission, four days after the first hemoptysis, shows a rounded shadow of increased density in the lower portion of the right pulmonary field just above the diaphragm. There is a slight haziness beside and below this shadow. *B*, in a roentgenogram made two months later the round shadow is less dense and is sharply demarcated. Some retraction at its upper border is due to partial healing and to replacement by scar tissue.



Fig 8 (case 5)—Two years later the shadow in the lower portion of the right lung has been replaced by a stellate scar of fibrous tissue. Lobar pneumonia would not leave such a residual scar, by this criterion the two processes may be differentiated.

the right lung, and many smaller, more recent infarcts in the remainder of the right lung

The infarct, which was present in the lower lobe of the right lung at the time the roentgenogram was made, was, despite its size, obscured by the passive hyperemia and the large cardiac shadow

CASE 5—F Y, a white man aged 49, was admitted to the medical service on Feb 8, 1938. Four months before admission he had sustained a fracture of the right tibia. The right leg had been placed in a cast for about one month. Nineteen days before admission severe pain developed in the right side of the chest, and two days later the patient had a small hemoptysis, with some streaking of the blood, which recurred until the time of admission. Four days before admission he noticed swelling of the right leg. On admission there were signs of consolidation in the lower lobe of the right lung and of thrombophlebitis in the right thigh. A roentgenogram made at this time revealed an ovoid shadow of increased density, with slightly feathered edges (fig 7A).

After a prolonged period of elevated temperature the physical signs in the lung and the thrombophlebitis subsided. A roentgenogram made on the fifty-sixth day of hospitalization (fig 7B) showed the same shadow, of the same size but of less density. Some streaked fibrous changes were noted. The patient was discharged, asymptomatic, on the eighty-second day.

Two years later another roentgenogram of the chest (fig 8) showed a stellate scar in the same area, just above the right half of the diaphragm. This scar tissue represented the final healing of the infarct and illustrates the fact that pulmonary infarct, unlike lobar pneumonia, will often leave a scar which will persist for years.

SUMMARY AND CONCLUSIONS

In 6,548 cases in which autopsy was done, 344 cases of aseptic hemorrhagic infarction of the lung were observed, an incidence of 5.2 per cent.

In 174 instances, or 2.7 per cent, the pulmonary infarct was a significant cause of death.

Infarction is a far more serious complication in the course of heart disease than in its absence.

Hemoptysis is the most frequently noted symptom. The physical signs vary considerably and are modified by the presence of secondary infection or pleural effusion.

There is no single typical roentgenologic picture of pulmonary infarction. Roentgenograms taken in more than one projection will aid considerably in making the diagnosis.

In our series a correct diagnosis was made in 22 per cent of the cases in which the infarct was an important cause of death.

THE COLD PRESSOR AND THE BREATH-HOLDING TEST

AN ANALYSIS OF RESULTS IN TWO HUNDRED SUBJECTS

ROBERT H FELDT, M D

AND

D E W WENSTRAND, M D

MILWAUKEE

Blood pressure rises in response to many stimuli in both normal and hypertensive persons. It is well known that the response is greater in patients with essential hypertension than it is in normal persons. In an attempt to devise a standard stimulus for measuring this reaction, Hines and Brown¹ developed the cold pressor test.

More recently Ayman and Goldshine² described a breath-holding test for use as a standard blood pressure stimulus. They concluded that there was a "striking similarity" in the reactions of the blood pressure to the cold pressor and breath-holding tests. In their series the breath-holding test, as a general rule, showed a greater reaction. Since the breath-holding test requires no special equipment, Ayman and Goldshine felt it might well be used in place of the cold pressor test. In order to compare the two tests, the reactions of 200 persons, some with normal and some with elevated blood pressures, have been observed.

TECHNIC OF TESTS

The exact technic of Hines³ was used for the cold pressor test. The subject reclined in a quiet room for a period of twenty to sixty minutes. Blood pressure determinations were made at intervals until a basal level was reached. A longer rest period is usually required in hypertensive patients. The cuff of the sphygmomanometer remained on one arm, and after the basal level was reached, the opposite hand was plunged into water at a temperature of 3 to 5 C (37.6 to 41 F). The hand was kept immersed to just above the wrist for sixty seconds. The blood pressure was determined at thirty seconds and sixty seconds.

After the cold pressor test was finished, and the blood pressure had returned to the basal level, the breath-holding test was given. The only deviation from

From the Medical Department Northwestern Mutual Life Insurance Company

1 Hines, E A, Jr, and Brown, G E. A Standard Stimulus for Measuring Vasomotor Reactions, *Proc Staff Meet, Mayo Clin* 7:332 (June 8) 1932.

2 Ayman, D, and Goldshine, A D. The Breath-Holding Test. A Simple Standard Stimulus of Blood Pressure, *Arch Int Med* 63:899 (May) 1939.

3 Hines, E A, Jr. Technic of the Cold Pressor Test, *Proc Staff Meet, Mayo Clin* 14:185 (March 22) 1939.

the technic of Ayman and Goldshine was that the subject was kept in a supine position throughout the test instead of the sitting position. The subject was instructed to place his free arm on his chest and cautioned not to take deep breaths in anticipation of the breath holding. The moment quiet expiration was observed, he was instructed to stop breathing and to cover his nose and mouth with his free hand to prevent the passage of air. The pressure in the cuff was raised to the systolic level and kept there. Exactly at the end of twenty seconds, the systolic reading was taken. The subject was told to breathe normally, and a new basal level was determined. The procedure was then repeated except that this time the diastolic blood pressure was read at the end of the twenty seconds.

In our experiments both tests were explained to the subject at the beginning of the rest period. The breath holding just described was practiced sufficiently to insure exact cooperation.

EXPLANATION OF TERMS

With either test the difference between the basal level and the maximum reading is said to be the range, reaction or response. Subjects

TABLE 1—*Results of Cold Pressor and Breath-Holding Tests in Two Hundred Subjects*

Group	Cold Pressor Test				Breath Holding Test		
	Sub jects	Mean Rise of Blood Pressure in Millimeters of Mercury		Sub jects	Mean Rise of Blood Pressure in Millimeters of Mercury		
		Systolic	Diastolic		Systolic	Diastolic	
Normal hyporeactors	128	10.91 \pm 0.28	12.49 \pm 0.34	151	13.23 \pm 0.23	12.19 \pm 0.30	
Normal hyperreactors	57	28.09 \pm 0.62	24.30 \pm 0.55	34	26.85 \pm 0.69	21.71 \pm 0.64	
Hypertensive subjects	15	31.93 \pm 2.44	20.87 \pm 1.96	15	28.47 \pm 2.51	21.47 \pm 1.69	
All subjects combined	200	17.38 \pm 0.52	16.49 \pm 0.40	200	16.73 \pm 0.42	14.50 \pm 0.34	

with normal blood pressure whose reaction did not exceed 20 mm systolic and 15 mm diastolic were called normal hyporeactors or normal reactors. Normal hyperreactors were those persons with normal blood pressure who showed a reaction exceeding 20 mm systolic and 15 mm diastolic.

SUBJECTS OF TESTS

The cold pressor and breath-holding tests were performed on 185 persons with normal blood pressure and 15 subjects who had elevated blood pressure. All of them were regularly employed in clerical positions. Among the normal subjects there were 137 men and 48 women, the average age of the group was 37.1 years. All of the hypertensive persons were men, the average age was 52 years. The blood pressure was arbitrarily said to be elevated if it was over 145 systolic and/or 95 diastolic after twenty minutes or more of rest in a reclining position. Most of the hypertensive subjects showed blood pressures well above these figures while at rest. No classification was made according to the degree of hypertension, the cause of the hypertension or the secondary cardiovascular-renal changes.

RESULTS OF TESTS

The results are summarized in table 1. Among the 185 subjects with normal blood pressure, 128 (69.2 per cent) gave a hyporeaction to the cold pressor test and showed an average response of 10.91 ± 28 mm⁴ systolic and 12.49 ± 34 mm diastolic. By comparison, 151 (81.6 per cent) of those with normal blood pressure showed a hyporeaction to the breath-holding test, and the average response was 13.23 ± 23 mm systolic and 12.19 ± 30 mm diastolic. There were 57 (30.8 per cent) normal hyperreactors to the cold pressor test, the average rise was 28.09 ± 62 mm systolic and 24.30 ± 55 mm diastolic. Thirty-four (18.4 per cent) normal hyperreactors to the breath-holding test showed an average rise of 26.85 ± 69 mm systolic and 21.71 ± 64 mm diastolic. Among the subjects with hypertension the average response to the cold pressor test was 31.93 ± 2.44 mm systolic and 20.87 ± 1.96 mm diastolic. The average response to breath holding was 28.47 ± 2.51 mm systolic and 21.47 ± 1.69 mm diastolic.

COMPARISON OF THE BREATH-HOLDING AND COLD PRESSOR TESTS

The breath-holding test produces a rise in blood pressure, and the cold pressor test produces a rise in blood pressure, but it cannot be said from our results that a "striking similarity" exists in the degree of response. If the arithmetic mean is used in making comparison, the reactions to the two tests do show a remarkable similarity, as seen in table 1. When all 200 subjects, hypertensive persons and those with normal blood pressure, were studied, the mean systolic response to the cold pressor test was 17.38 ± 52 mm and 16.73 ± 42 mm to the breath-holding test. The mean diastolic reaction in the 200 persons was 16.49 ± 40 mm to cold and 14.50 ± 34 to breath holding.

In only one classification was the difference between reactions to the two tests statistically significant.⁵ Among normal hyporeactors to the two tests the systolic response to the breath-holding test exceeded the response to the cold pressor by 5.9 times the probable error. It is difficult to evaluate the significance of this difference, and further study will be necessary to determine whether breath holding really produces a greater systolic response in normal hyporeactors.

4 The figure after the sign is the probable error of the arithmetic mean.

5 Statisticians do not consider a difference between two arithmetic means as "significant" unless it is at least 4 times the probable error in the difference of the two means. The probable error in the difference of two means is equal to the square root of the sum of the squares of the probable errors of the two means. A difference of 4 times the probable error can occur once in 142 times as a matter of chance.

As shown in table 2, individual variations occurred frequently. For example, among normal hyperreactors to the cold pressor test the breath-holding test gave a greater diastolic reaction than the cold pressor test in only 3 (5.3 per cent), while the cold pressor test gave a greater reaction in 41 (71.9 per cent). Among normal hyporeactors to the cold pressor test the breath-holding test gave a greater diastolic reaction in 36 (28.1 per cent), and the cold pressor test gave a greater diastolic reaction in 31 (24.2 per cent). For all 200 subjects the breath-holding reaction was higher in 26.5 per cent systolic and 21.5 per cent diastolic. The cold pressor reaction was higher in 31 per cent systolic and 38.5 per cent diastolic. The cold pressor reaction was the same⁶ as the breath-holding reaction in 42.5 per cent systolic and 40 per cent diastolic.

TABLE 2—*Comparison of Blood Pressure Reactions to Cold Pressor and Breath-Holding Tests*

Comparison	All 200 Subjects				128 Normal Hyporeactors to Cold				57 Normal Hyperreactors to Cold				15 Hypertensive Subjects			
	Systolic		Diastolic		Systolic		Diastolic		Systolic		Diastolic		Systolic		Diastolic	
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
Reaction to breath holding greater	53	26.5	43	21.5	47	36.7	36	28.1	3	5.3	3	5.3	3	20	4	26.7
Reactions to breath holding and cold the same	85	42.5	80	40.0	64	50.0	61	47.7	15	26.3	13	22.8	6	40	6	40.0
Reaction to cold greater	62	31.0	77	38.5	17	13.3	31	24.2	39	68.4	41	71.9	6	40	5	33.3

It is impossible to make a brief tabular analysis of individual differences between the responses to the two tests. Among hypertensive subjects the difference between the response to the cold pressor test and that to the breath-holding test in the same person was at times as great as 20 or 25 mm. Among hyperreactors differences of 10 mm or more between the responses to the two tests were common.

Although we found 16 hyperreactors to the breath-holding test among 128 normal hyporeactors to the cold pressor test, wide differences were unusual. Of only 4 of the 16 persons could it be said that the cold pressor test gave little or no reaction (diastolic response below 10 mm). Among 151 normal hyporeactors to the breath-holding test there were 39 who were hyperreactors to the cold pressor test. In 8 of the 39 persons the diastolic response to breath holding was below 10 mm.

⁶ The responses to the cold pressor and breath-holding tests were considered the same if the difference between them was less than 5 mm.

COMMENT

The foregoing comparison shows that in our series the responses to cold and breath holding were similar when the arithmetic means were compared. The only significant difference in arithmetic means between the two tests was among normal hyporeactors, in whom the breath-holding test gave a greater systolic response. In the entire group the reaction to the cold pressor was the same as or greater than the reaction to the breath-holding test in 73.5 per cent of the systolic readings and 78.5 per cent of the diastolic readings. There were wide individual differences. Ayman and Goldshine stated that some of their subjects showed little or no reaction to the cold pressor but were hyperreactors to the breath-holding test. A few of our subjects showed the same phenomenon, hyperreaction to breath holding but hyporeaction to cold. A much larger number showed just the reverse, hyporeaction to the breath-holding test and hyperreaction to the cold pressor test.

In our experience, with subjects whose intelligence is presumably above average, full cooperation was had for all the breath-holding tests. It is conceivable that this might not always be obtainable. Certainly the test is not adaptable to dyspneic patients, as Ayman and Goldshine pointed out. While the material necessary for a cold pressor test is not always available, this disadvantage is compensated by the fact that a minimum of cooperation is required for its successful completion.

So far we have not been able to confirm all the results obtained by Ayman and Goldshine. We are continuing our studies. Much more evidence will have to be accumulated before it can be said that one test is better than another as a stimulus for measuring blood pressure reactions.

SUMMARY

In the present series of 200 cases the mean responses of the blood pressure to the cold pressor test and the breath-holding test were similar except that breath holding obtained a slightly greater systolic reaction among normal hyporeactors. In most of our subjects the response to the cold pressor test was the same as or higher than the response to the breath-holding test. Wide differences between the reaction to the cold pressor test and the reaction to the breath-holding test were at times found in the same person. Hyperreaction to cold was found in 39 subjects who were hyporeactors to breath holding. Hyperreaction to breath holding was found in 16 subjects who were hyporeactors to cold.

THROMBOSIS OF THE COMMON, INTERNAL AND EXTERNAL CAROTID ARTERIES

A REPORT OF TWO CASES WITH A REVIEW OF THE LITERATURE

MORTON GALDSTON, M D

SIDNEY GOVONS, M D

S BERNARD WORTIS, M D

J MURRAY STEELE, M D

AND

HENRY K TAYLOR, M D

NEW YORK

Recently Egas Moniz¹ and Sörgo,² after making cerebral arteriographic studies, suggested that thrombosis of the internal carotid artery at its origin is more frequent than is generally supposed. However, unilateral thrombosis of the common and internal carotid arteries without involvement of the subclavian artery and the associated inequality of radial pulses and blood pressures in the two arms is rare. We found reports of only 11 such cases in the literature. Sörgo² encountered occlusion of the internal carotid artery in 8 patients and confirmed his diagnosis of this condition in 2 by postmortem examinations. He was able to find 20 more cases by a search of the literature. Thrombosis of the internal carotid artery has been found at autopsy,³ and Saphir^{3c} stressed the importance of searching for obstruction to the internal carotid artery in

From the Third (New York University) Division of Welfare Hospital for Chronic Diseases

Read before the Section of Neurology and Psychiatry of the New York Academy of Medicine, Dec 10, 1940

1 Egas Moniz, Almeida Lima, and de Lacerda, R. Hemiplegies par thrombose de la carotide interne, *Presse med* **45** 977, 1937

2 Sörgo, W. Ueber den durch Gefassprozesse bedingten Verschluss der Art carotis interna, *Zentralbl f Neurochir* **4** 161, 1939

3 (a) Forti, F. Emplegia per trombose della carotide interna in corso di tifo, *Riv di clin med* **31** 425, 1930 (b) Arteriosclerosis of Internal Carotid Arteries. Cerebral Infarcts, Cabot Case 19471, *New England J Med* **209** 1063, 1933 (c) Saphir, O. Serpentine Aneurysm of the Internal Carotid Artery with Resulting Encephalomalacia and Cerebral Hemorrhage, *Arch Path* **20** 36 (July) 1935 (d) Dial, D L., and Maurer, G B. Intracranial Aneurysms. Report of Thirteen Cases, *Am J Surg* **35** 2, 1937

the carotid canal and the cavernous sinus (sites which are commonly overlooked at autopsy) in every instance of encephalomalacia and cerebral hemorrhage⁴ Congenital narrowing⁵ and, in some instances, absence of one common carotid artery have also been reported⁶

Hemiplegia due to thrombosis of the common and internal carotid arteries of one side appears to be rare, perhaps, as Hunt⁷ suggested, because "these vessels are frequently ignored both in clinical and pathological studies" Recently, 2 patients out of 100 with hemiplegia in the wards of Welfare Hospital for Chronic Diseases were shown to have thrombosis of the carotid arteries of the left side Both patients had a hyperactive carotid sinus reflex on the side on which the artery was patent

REPORT OF CASES

CASE 1—R S, a 52 year old white man, while at work on July 20, 1938, suddenly lost his ability to speak and to use his arms and legs He was taken to Morrisania City Hospital, where it was learned from his wife and friends that he had always been healthy except for pneumonia at the age of 30 Observation there revealed spastic hemiplegia of the right side with sensory and motor aphasia, variable arterial pressure (between 210 systolic and 150 diastolic and 180 systolic and 100 diastolic) without cardiac enlargement or renal impairment, and moderate sclerosis of the retinal arteries The cerebrospinal fluid showed normal dynamics, and its content of sugar and protein and number of cells was normal The blood and spinal Wassermann reactions were negative The course of his illness was uneventful

On July 6, 1939 he was transferred to the neuropsychiatric service of the Third (New York University) Division of Welfare Hospital for Chronic Diseases

The physical examination on admission gave essentially the same results as at Morrisania City Hospital In addition, the medical consultant noted a bilateral patchy flush of the skin on the face, neck and upper part of the chest, a mottled livid color of the lower parts of the legs and the arms coexistent with coldness and perspiration, and considerable dermatographia There was moderate sclerosis of the peripheral vessels Of greatest interest was the absence of pulsation in the left

4 Other sites which should be carefully examined, according to Saphir are the vertebral arteries and the circle of Willis, particularly for evidence of congenital anomalies

5 Smith, H L, and Hinshaw, H C Syncopal Attacks Due to Congenital Anomaly of Right Common Carotid Artery, *Am Heart J* **11** 619, 1936 Elliot, A H, Ussher, N T, and Stone, C S Bilateral Denervation in a Patient Having Syncopal Attacks and Congenital Vascular Anomaly Unusual Case, *ibid* **17** 69, 1939

6 Boyd, J D Absence of Right Common Carotid Artery, *J Anat* **68** 551, 1934

7 Hunt, R The Role of the Carotid Arteries in the Causation of Vascular Lesions of the Brain, with Remarks on Certain Special Features of the Symptomatology, *Am J M Sc* **147** 704, 1914

internal, external and common carotid and temporal arteries Bradycardia, sharp fall in arterial pressure and generalized tonic and clonic convulsive seizures occurred on pressure over the right carotid sinus There was only slight slowing of the pulse on pressure over the left carotid sinus (fig 1*A* and *B*) Arterial pressure was the same in both arms The diagnosis was (1) probable thrombosis of the left common, external and internal carotid arteries with right hemiplegia and mixed aphasia, (2) right hyperactive carotid sinus reflex and (3) hypertension, probably of the diencephalic type

The patient's condition has remained unchanged since admission to Welfare Hospital for Chronic Diseases An occasional generalized convulsive seizure,

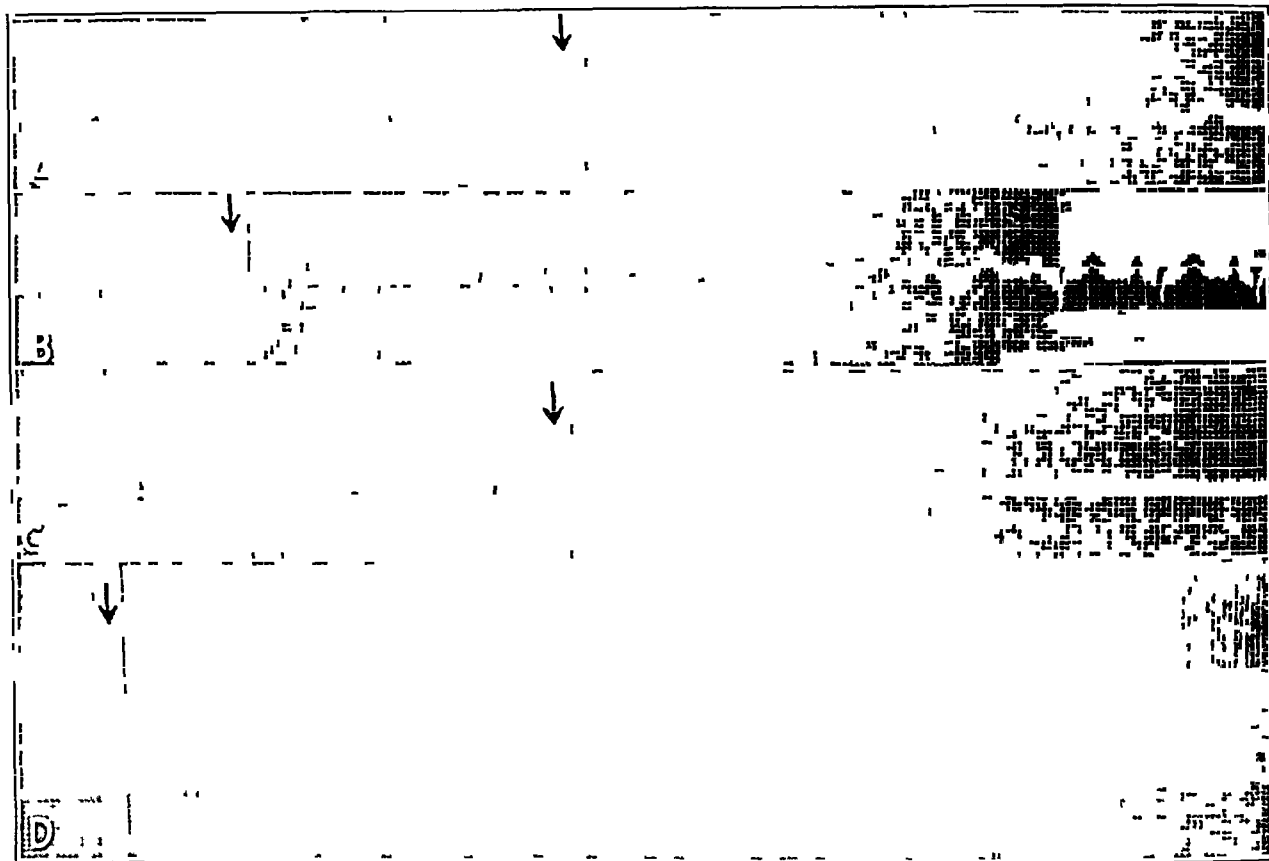


Fig 1—In *A* (case 1), pressure over the right carotid sinus was begun at arrow and maintained for seven seconds, causing slowing of the heart from 90 to 50 beats a minute In *B* the arrow indicates release of pressure with gradual return to original rate In *C* (case 2), pressure over the right carotid sinus was begun at arrow and maintained for six seconds In *D* the arrow indicates release of pressure, with asystole for six and one-half seconds

during which he did not lose control of his sphincters or bite his tongue, has occurred Examination in most instances was made a few minutes after the seizure began and revealed a regular, rapid pulse rate and arterial pressure of 200 systolic and 120 diastolic

The roentgen shadow of the heart was not enlarged The aorta was tortuous and sclerotic The cardiac chambers, visualized by the Robb-Stenberg technic,

were of normal size. The right, but not the left common, carotid artery was visualized (fig 2).

Roentgenograms of the skull showed a calcified pineal gland, displaced slightly backward. The bony cage was not abnormal. An encephalogram revealed bilateral hydrocephalus with a multilocular cyst involving the anterior half of the left cerebrum and communicating with the left ventricle (fig 3). A direct injection of 10 cc of colloidal thorium dioxide into the right common carotid artery (fig 4) showed that only the vessels of the right cerebral hemisphere could be well visualized. The contrast medium did not pass to the left cerebral hemisphere, even when it was introduced into the exposed right common carotid artery. Electro-

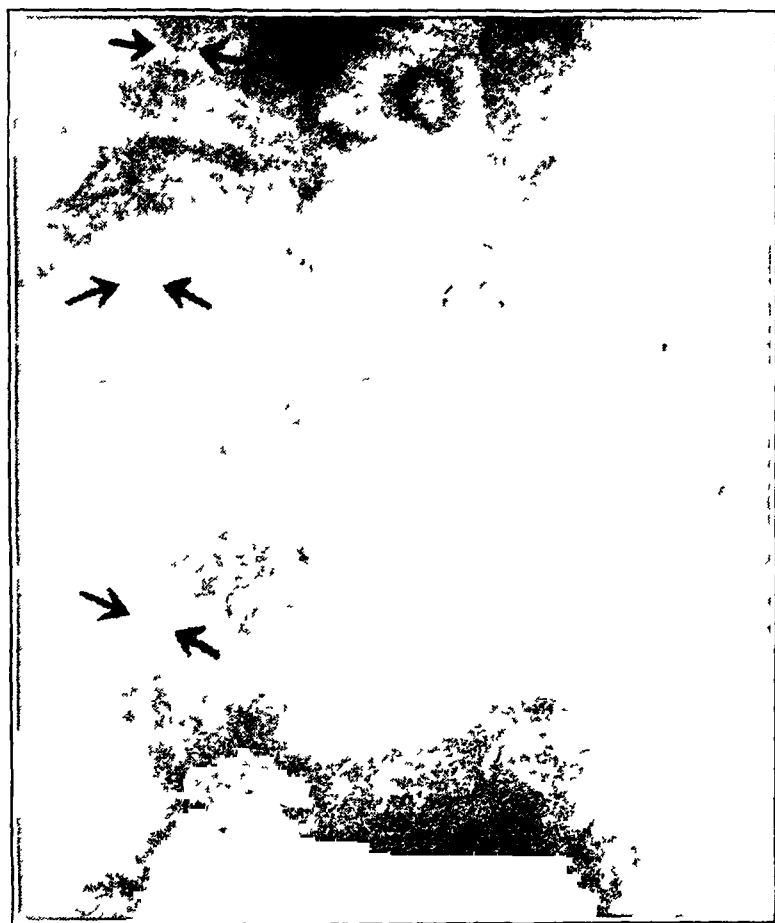


Fig 2 (case 1)—The contrast substance is visualized in the right common carotid artery (indicated by arrows).

encephalograms, made by Dr Hans Strauss, showed spontaneous abnormal activity over the left frontomotor region. After stimulation of the carotid sinus there was abnormal activity of an equal degree in both frontomotor regions.

After these preliminary observations, the vessels of the left side of the patient's neck were explored by Dr W F Ruggiero. The common and internal carotid arteries were found to be thrombosed throughout their course in the neck. A needle was inserted into the thoracic part of the common carotid artery for about 5 cm without obtaining blood, demonstrating that the thrombus extended at least this distance downward. The external carotid artery was thrombosed in

only the first 2 cm , the lingual and external maxillary arteries were patent and probably furnished part of the collateral circulation The entire cervical part of the common and internal carotid arteries and the external carotid artery below



Fig 3 (case 1) —The encephalogram shows bilateral hydrocephalus and a multilocular cyst in the anterior half of the left cerebrum, communicating with the left ventricle

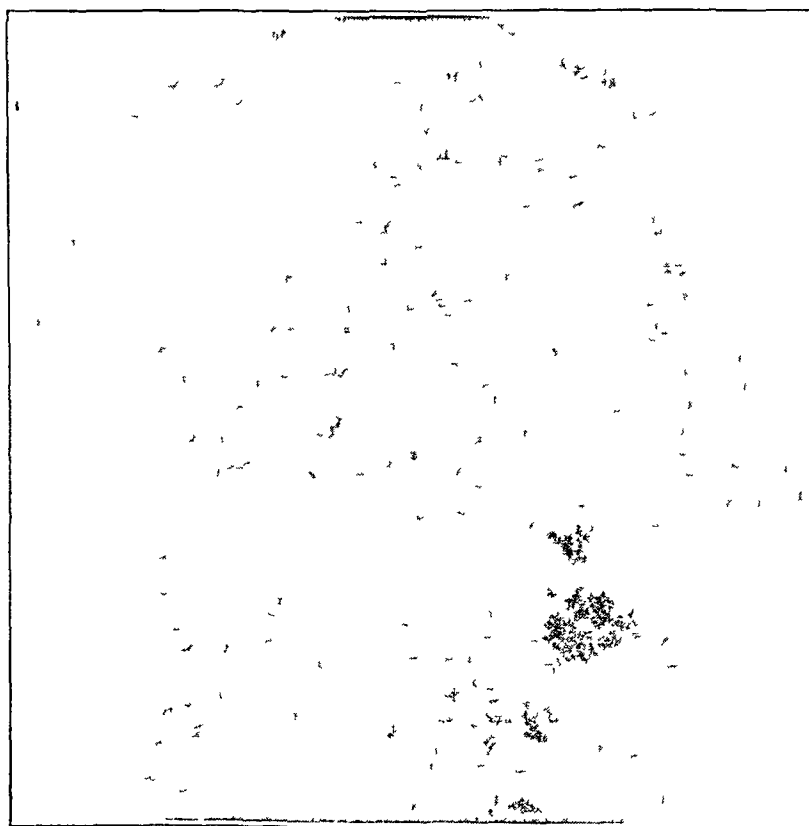


Fig 4 (case 1) —In this cerebral arteriogram the right internal carotid artery and the cerebral vessels are visualized There is no cross circulation to vessels of the opposite hemisphere

the origin of its lingual branch were removed. Gross and microscopic examination showed thrombosis of these arteries with evidence of arteriosclerosis. The first 1 or 2 cm of the external carotid artery only and its superior thyroid branch were occluded (fig 5A and B).

Laboratory Data—The urine was normal. The concentration test gave a specific gravity of 1.026. The urea clearance test (Van Slyke) revealed elimination 78 and 76 per cent of normal during two successive hours. The phenolsulfonphthalein test showed 35 per cent excreted during the first hour and 20 per cent during the second hour. An intravenous pyelogram did not show any abnormalities in the urinary tract.

The red blood cells numbered 5,100,000 per cubic millimeter, the hemoglobin was 14.4 Gm per hundred cubic centimeters. There were 10,200 white blood corpuscles per cubic millimeter, with a normal differential count. Sugar was

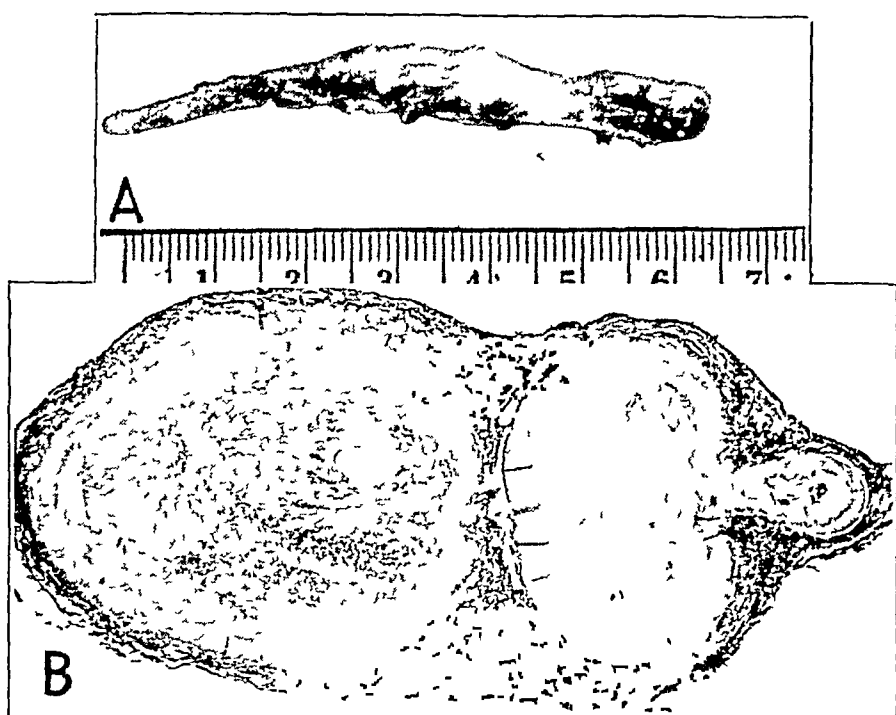


Fig 5 (case 1)—Cervical portions of the thrombosed common and internal carotid arteries and the first centimeter of the thrombosed external carotid artery and its superior thyroid branch. B, photomicrograph of a cross section through the internal carotid artery and the external carotid artery and its superior thyroid branch.

70 mg per hundred cubic centimeters, urea nitrogen, 12.6 mg, calcium, 10.6 mg, phosphorous, 3 mg, and total cholesterol, 207 mg. The total protein was 6.5 Gm, albumin, 4.5 Gm, and globulin, 2.0 Gm, per hundred cubic centimeters. The Kahn and Wassermann reactions of the blood were negative.

The cerebrospinal fluid showed normal dynamics and absence of cells. The result of a qualitative test for sugar was normal, and the Pandy and Wassermann tests were negative. There was 56 mg of protein per hundred cubic centimeters.

The basal metabolic rate was —5 per cent.

CASE 2—E. G., a 52 year old white man, on Feb 21 1940 was found lying on the street, confused and scarcely able to talk. He was brought by ambulance to Bellevue Hospital.

On admission he was confused and irrational. The arterial pressure was 190 systolic and 110 diastolic, the pulse rate was rapid and regular, the heart was otherwise normal. There were slight weakness of the right arm and leg, absence of abdominal reflexes on the right and absence of knee jerk reflexes on both sides. The ocular fundi exhibited moderate arteriosclerosis. The examinations of the urine, blood and spinal fluid, including the Wassermann tests, gave normal results.

The hospital records show that four years previously (June 25, 1936) he had been admitted to the hospital after a similar occurrence and had been discharged in two days. The diagnosis then had been (1) syncope of unknown cause, (2) essential hypertension and (3) hypertensive and arteriosclerotic heart disease.

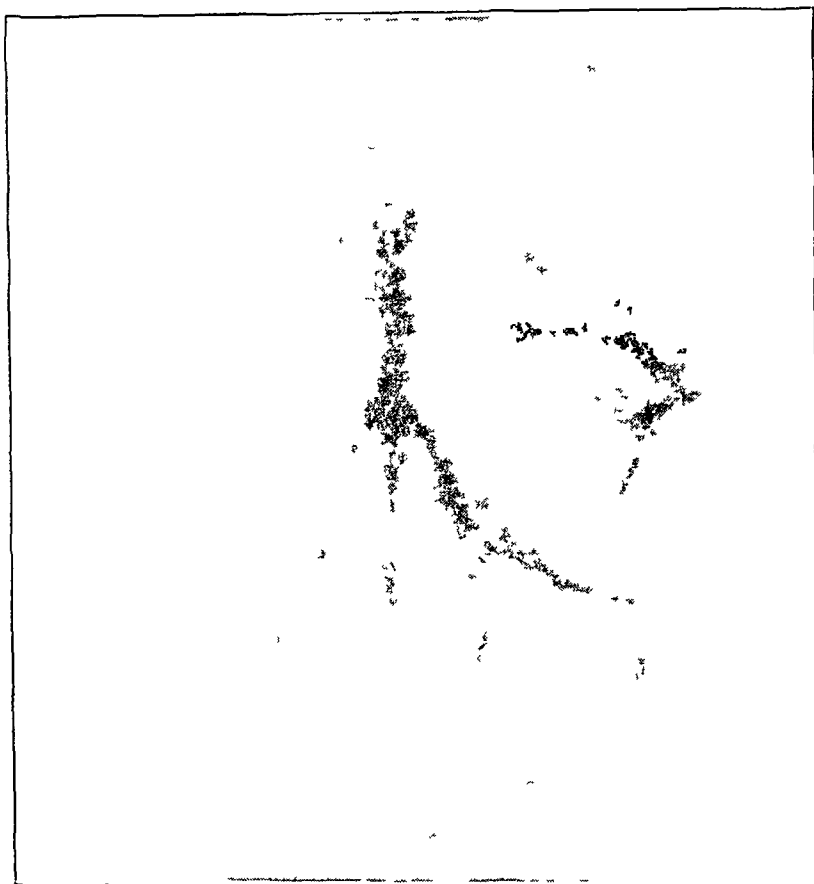


Fig 6 (case 2) —In this cerebral arteriogram the right internal carotid artery and a direct communication between the cerebral vessels of both hemispheres are visualized.

with paroxysmal auricular fibrillation. At that time he described his seizures as preceded by dizziness, coughing up of white mucoid sputum and generalized shaking. He did not know how long he remained unconscious and always felt dizzy for one to two days after each seizure. During these attacks he did not lose control of his sphincters or bite his tongue. The seizures began at the age of 34 and occurred as often as six or seven times a month. Occasionally, there would be a free interval of eight or nine months.

On the sixty-fifth day of hospitalization (April 26, 1940), the patient was transferred to the Third (New York University) Medical Division of Welfare Hospital for Chronic Diseases. The diagnosis at that time was (1) left cerebral

thrombosis with right hemiplegia and mixed aphasia, (2) idiopathic epilepsy and (3) generalized and cerebral arteriosclerosis

On physical examination at Welfare Hospital for Chronic Diseases, additional observations of considerable interest were made. Pulsation of the left common, external and internal carotid arteries was absent. Pulsation of the left temporal artery was present. Light pressure over the right carotid sinus resulted in asystole for a few seconds (fig 1 C and D), sharp fall in arterial pressure, loss of consciousness and a generalized tonic and clonic convulsive seizure. Pressure over the left carotid sinus was associated with only slight slowing of the heart rate. There was a defect in the right upper homonymous quadrantic visual field. Pulsations of the vessels of the upper and lower extremities were equal and normal. The radial arteries showed a moderate degree of sclerosis. The arterial pressure was 130 systolic and 70 diastolic in both arms.

The diagnosis was (1) thrombosis of the left common, external and internal carotid arteries with right hemiplegia and mixed aphasia, (2) hypersensitivity of the right carotid sinus and (3) generalized arteriosclerosis.

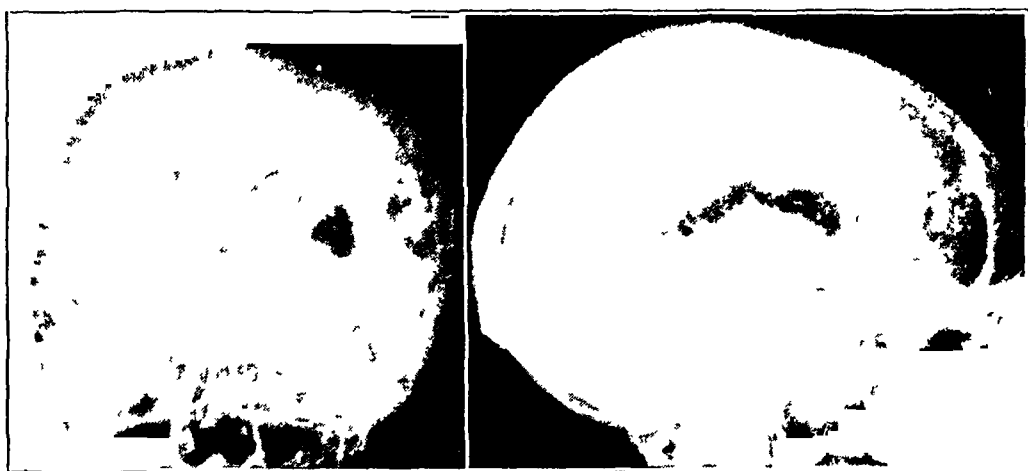


Fig 7 (case 2) —This encephalogram shows slight dilatation of the ventricular system, particularly the left lateral ventricle, without displacement. Cortical atrophy is more marked on the left side.

Since admission to this hospital he has not had any spontaneous convulsive seizures, and his general condition has remained unchanged. His arterial pressure has ranged between 210 systolic and 110 diastolic and 130 systolic and 80 diastolic. Roentgenograms showed the chest and heart were normal. The cardiac chambers as visualized by the Robb-Steinberg technic were normal. The vessels of the lower extremities and abdominal portion of the aorta were shown by a roentgenogram to be partially calcified.

A cerebral arteriogram made on May 10, 1940 by an injection of 10 cc of colloidal thorium dioxide into the right common carotid artery revealed a direct communication between the cerebral vessels of the two hemispheres (fig 6). This was interpreted by one of us [H K T] as suggestive of occlusion of the left internal carotid artery. The cerebral vessels appeared normal.

An encephalogram made on May 14 indicated slight dilatation of the entire ventricular system, particularly the left lateral ventricle, without displacement, and cortical atrophy, particularly on the left side (fig 7).

After these observations were made, surgical exploration of the left side of the patient's neck, performed by Dr W F Ruggiero, revealed that the entire

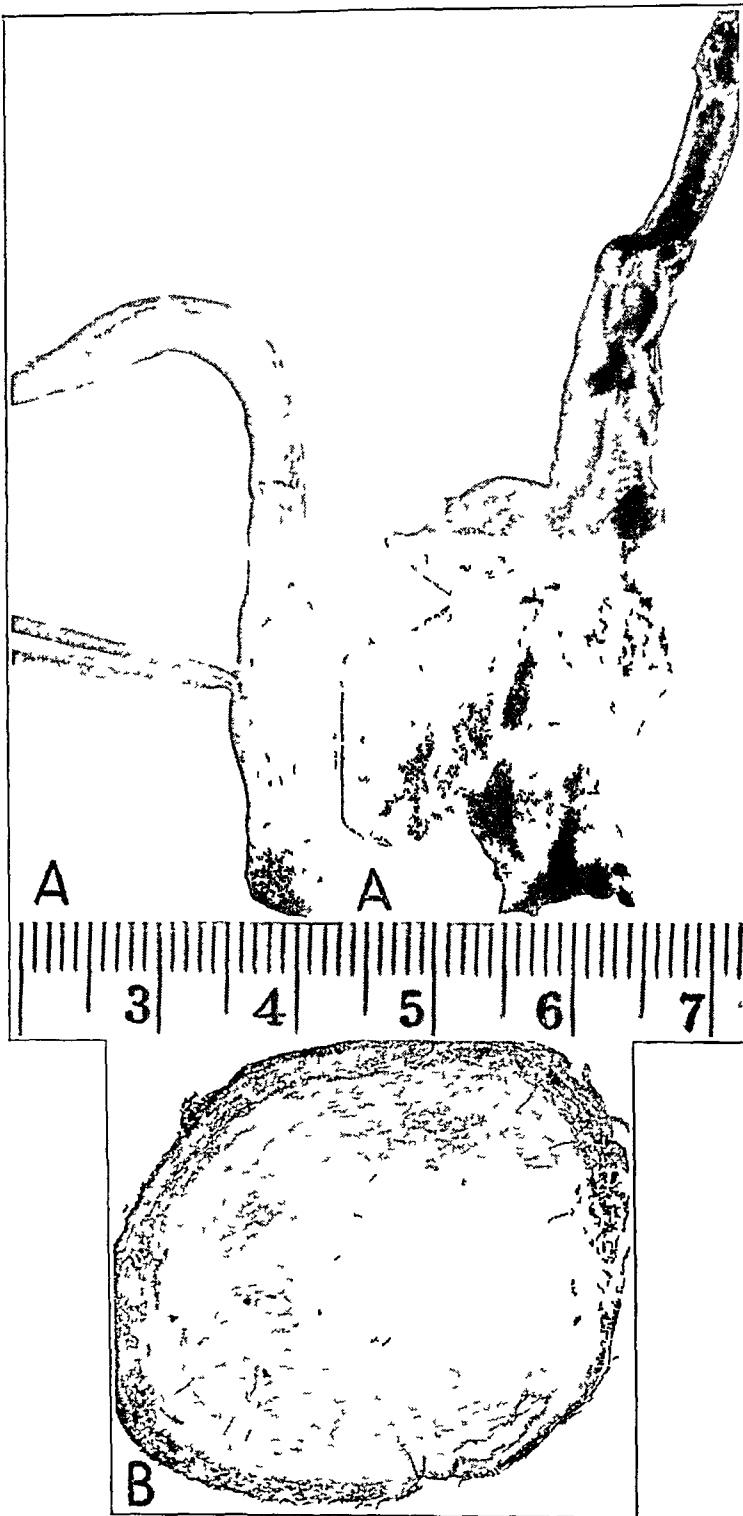


Fig 8 (case 2) —*A*, cervical portions of the thrombosed common and internal carotid arteries and the first 2 cm of the external carotid artery. The vessels were opened, and the thrombus pushed to one side, exposing the intimal surface. *B*, photomicrograph of a cross section of the thrombosed common carotid artery just below the carotid bifurcation.

cervical part of the common and internal carotid arteries and the first few centimeters of the external carotid artery were thrombosed. The remainder pulsed feebly. The entire cervical part of the internal and common carotid arteries was removed, and the external carotid artery was sectioned just beyond the carotid bifurcation. A needle was thrust into the thoracic portion of the common carotid artery for a distance of about 5 cm without obtaining blood, indicating that the thrombus extended at least this distance downward.

Gross and microscopic study of the arteries showed thrombosis of the common, internal and external carotid arteries and arteriosclerotic changes. Only the first centimeter or two of the external carotid artery was occluded (fig 8).

Laboratory Data—The urine was normal. The urea clearance test (Van Slyke) revealed elimination 145 per cent of normal in the first hour and 101 per cent of normal in the second hour. The phenolsulfonphthalein test showed excretion of 37 per cent in the first hour and of 8 per cent in the second hour.

The red blood corpuscles numbered 4,920,000 per cubic millimeter, the hemoglobin content was 16 Gm per hundred cubic centimeters. There were 10,500 white blood corpuscles per cubic millimeter, with a normal differential count. The Kahn and Wassermann reactions of the blood were negative. Urea nitrogen in the blood was 147 mg and sugar 86 mg per hundred cubic centimeters.

The cerebrospinal fluid showed normal dynamics, the Pandy and Wassermann tests were negative, and the colloidal gold curve was 0000111100. There was 46 mg of protein per hundred cubic centimeters of spinal fluid, and no cells were seen on microscopic examination.

The basal metabolic rate was — 12 per cent.

COMMENT

Causes of thrombosis of the carotid arteries are not clear since pertinent data and microscopic descriptions of the vessels are frequently omitted in case reports.⁸ Sclerosis of the aorta⁹ and pressure from an aortic aneurysm appear to be the phenomena most commonly associated with thrombosis of the carotid arteries.⁷ Obliterating syphilitic arteritis without aneurysm,¹⁰ embolism¹¹ and nonsyphilitic arteritis¹² have been reported in a few instances.

8 This paper does not deal with thrombosis following trauma or ligation of these vessels.

9 Poppich, G. Ueber nicht thrombotischen Verschluss der grossen Gefassostien des Aortenbogens, insbesondere des Ostiums der Carotis communis sinistra, Frankfurt Ztschr f Path **25** 236, 1921.

10 Darling, S. T., and Clark, H. C. Arteritis Syphilitica Obliterans, J. M. Research **32** 1, 1915.

11 (a) Cohn, B. Einfache nicht complicirte Embolie der grossern Hirnarterien. A. Der Carotis communis, in Klinik der embolischen Gefasskrankheiten, Berlin, August Hirschwald, 1860, p. 364. (b) Fraenkel, E. Ueber zwei durch totalen Verschluss der linken Carotis complicirte Aneurysmen des Aortenbogens, Virchows Arch f path Anat **79** 509, 1880. (c) Eichhorst, H. Ueber Emboli der Carotis communis, Med Klin **32** 885, 1907. (d) Haffner, S. Obliteration der Carotis communis sinistra und beider Arteriae brachialis in Folge von embolischer Arteritis bei Herzfehler, Deutsches Arch f klin Med **60** 523, 1898.

12 Harbitz, F. Bilateral Carotid Arteritis, Arch Path **1** 499 (April) 1926.

Sclerosis of the carotid arteries seems to be not uncommon even in young adults¹³ Egas Moniz¹ and Sörgo² have suggested the presence of severe sclerosis of the carotid arteries in some patients to account for obscure neurologic symptoms Keele^{13b} studied the pathologic changes in the carotid vessels and compared them with the alterations in the aortic arch and in the iliac and innominate arteries in 55 successive unselected cases in which postmortem examinations were made The ages ranged from 7 to 79 years The carotid sinuses of 50 of the 55 patients showed sclerotic changes Thirty-two of these, whose average age was 45 (ranging from 16 to 79 years), had slight to extreme fatty flecking of the carotid sinus, the remaining 18 patients, whose average age was 62 years (ranging from 42 to 76 years), had slight to extreme calcification The lower part of the carotid sinus was more frequently affected than the upper The common carotid artery was less frequently sclerotic than the carotid sinus, and the most noticeable changes occurred just below the point of bifurcation The angle of bifurcation also was commonly affected Sclerosis of the external carotid artery rarely occurred and then only at the points of origin of the branches The internal carotid artery was not involved to the "slightest degree" in any of the cases (Keele's observations appear to have been restricted to the cervical part of the internal carotid artery) The same degree of sclerosis was usually present in the aortic arch and in the innominate and common iliac bifurcation as in the carotid sinus and the upper end of the common carotid artery It is apparent that sclerosis of the vessels of the neck is part of a generalized process Dow¹⁴ and Saphir^{3c} have shown that appreciable sclerotic change in the internal carotid artery in its course through the carotid canal and cavernous sinus is not infrequent

The effect of ligation of the great vessels of the neck has been studied clinically and experimentally¹⁵ It has been stated that unilateral ligation or spontaneous occlusion of the common carotid artery is followed in 10 to 30 per cent of the cases by cerebral damage In spite of

13 (a) Beneke, R Die Atherosklerose der Carotis communis und ihre Bedeutung für das Verständnis der Blutsaulenformen, Frankfurt Ztschr f Path **28** 407, 1922 (b) Keele, C A Pathological Changes in the Carotid Sinus and Their Relation to Hypertension, Quart J Med **2** 213, 1933

14 Dow, R D The Incidence of Arteriosclerosis in the Arteries of the Body, Brit M J **2** 162, 1925

15 (a) Dorrence, G M Ligation of the Great Vessels of the Neck, Ann Surg **99** 721, 1934 (b) Pilcher, C, and Thuss, C Cerebral Blood Flow, Arch Surg **29** 1024 (Dec) 1934 (c) Wortis, H A Case of Cerebral Degeneration with Encephalographic Study Eight Years After Common Carotid Ligation, Am J M Sc **192** 517, 1936 (d) Shipley, A M, Winslow, N, and Walker, W W Aneurysm in the Cervical Portion of the Internal Carotid Artery An Analytical Study of the Cases Recorded in the Literature Between August 1, 1925 and July 31, 1936, Ann Surg **105** 673, 1937

the rich network of anastomoses between large cerebral arteries and the "endless continuous net" of cerebral capillaries, it is surprising that occlusion of one or even both common carotid arteries is not necessarily followed by cerebral symptoms ^{15a} Hunt ⁷ expressed the opinion that in most instances, "especially in young subjects with good hearts and elastic vessels," the collateral circulation through the circle of Willis is sufficient. More recently, however, Pilcher and Thuss ^{15b} were unable to find a correlation between the age of the subject, cerebral arteriosclerosis and cerebral complications following occlusion of the common carotid artery.

The evidences of spontaneous occlusion of one common carotid artery are various. As has been mentioned, clinical manifestations may be absent ¹⁰. Diminution of vision in the homolateral eye, ¹⁶ unilateral headache, ¹⁷ vertigo, ¹⁸ epileptiform ¹⁹ and convulsive seizures ²⁰ and mental deterioration have been described in the absence of neurologic signs. Hemiplegia is common and may be transient at its onset or may increase gradually, with or without sensory disturbance or aphasia ²¹. And yet

16 (a) Penzoldt, F. Ueber Thrombose (autochthone oder embolische) der Carotis, *Deutsches Arch f klin Med* **28** 80, 1881. (b) Baumler. Thrombotischer Hemiplegie infolge vom Verschluss der linken Karotis, *Munchen med Wchnschr* **54** 2500, 1907. (c) Raeder, J. G. Ein Fall von symmetrischer Karotisaffektion mit präseniler Katarakt und "Glaukom" sowie Gesichtsatrophie, *Klin Monatsbl f Augenh* **78** (supp) 63, 1927. (d) Marinesco, G., and Kreindler, A. Obliteration progressive et complete des deux carotides primitives, *Presse méd* **44** 833, 1936. (e) Egas Moniz, Almeida Lima and de Lacerda ¹. (f) Hunt ⁷. (g) Harbitz ¹².

17 Egas Moniz, Almeida Lima and de Lacerda ¹. Sorgo ². Hunt ⁷. Marinesco and Kreindler ^{16d}.

18 (a) Crawford, J. R. Bilateral Pulse Obliteration in Thoracic Aneurysm, *JAMA* **76** 1395 (May 21) 1921. (b) Kampmeier, R. H., and Neumann, V. F. Bilateral Absence of Pulse in the Arms and Neck in Aortic Aneurysm, *Arch Int Med* **45** 513 (April) 1930.

19 Penzoldt ^{16a}. Marinesco and Kreindler ^{16d}.

20 Sorgo ². Harbitz ¹². Marinesco and Kreindler ^{16d}.

21 (a) Savory, W. S. Case of a Young Woman in Whom the Main Arteries of Both Upper Extremities and Left Side of the Neck Were Throughout Completely Obliterated, *Med-Chir Tr* **39** 205, 1856. (b) Oppenheim, H. *Lehrbuch der Nervenkrankheiten*, Berlin, S. Karger, 1894, p. 517. (c) Erb, W. Ein Fall von ausgedehnter Gehirnerweichung bei totaler Obliteration der Carotis communis sinistra, *Munchen med Wchnschr* **51** 946, 1904. (d) Chao, W. H., Kwan, S. T., Lyman, R. S., and Loucks, H. H. Thrombosis of the Left Internal Carotid Artery, *Arch Surg* **37** 100 (July) 1938. (e) Egas Moniz, Almeida Lima and de Lacerda ¹. (f) Sorgo ². (g) Cohn ^{11a}. (h) Haffner ^{11d}. (i) Penzoldt ^{16a}. (j) Hunt ⁷.

obstruction of both common carotid arteries may occur with no more striking symptoms than dizziness and occasional syncope²²

The association of sensitivity of the carotid sinus and thrombosis of the carotid artery in these 2 patients is interesting. It is well known that the carotid sinus in arteriosclerotic persons is frequently sensitive to light external pressure and that a sensitive carotid sinus may be present without the person's ever having had episodes of syncope or related manifestations.

The history of one of our patients (case 2) strongly suggested that he had suffered from attacks of carotid sinus syncope since the age of 34. In both patients sensitivity of the carotid sinus was accompanied by a sharp fall in systolic and diastolic arterial pressure, marked slowing of the heart rate and generalized convulsive seizures.

In these 2 cases sensitivity of the carotid sinus and arteriosclerosis may have been mutually conducive to thrombus formation. Pronounced slowing of the blood stream for several seconds at a time together with irregularity and roughening of the intima of the internal and common carotid arteries would seem to present conditions generally recognized as conducive for thrombus formation.

Mention of examination for sensitivity of the carotid sinus was found in only 2 cases of carotid artery thrombosis. In one that of a person who suffered from "epileptiform seizures," unilateral stimulation of a carotid sinus was accompanied by convulsive seizures with little change in the arterial pressure and pulse rate^{18b}. Tests were made on only one carotid sinus, the other having been removed. In the other^{16b} there was only minimal response to stimulation of the thrombosed sinus, there was none to stimulation of the contralateral sinus.

It is interesting that in both our cases pulsations of the common, internal and external carotid arteries were not felt, and only in the second the patient (case 2) did the temporal artery of the thrombosed side pulsate. At operation we saw that both the common and internal carotid artery were thrombosed but that only the first 2 cm of the external carotid artery was thrombosed. The remainder of the vessel pulsated freely but feebly and apparently received blood from collateral vessels.

22 Yelloly, J. Case of Preternatural Growth in the Lining Membrane Covering the Trunks of the Vessels Proceeding from the Arch of the Aorta, *Med-Clin Tr* **12** 565, 1823. Broadbent, W. H. Absence of Pulsation in Both Radial Arteries, the Vessels Being Full of Blood, *Tr Clin Soc*, London **8** 165, 1875. Shikhare, P. V. Notes on the Remarkable Case of Absence of Pulsation in the Arteries of the Upper Parts of the Body, *Indian J Med* **2** 526, 1921. Cooley, L. E., and McNamara, F. P. Syphilitic Aortitis with Aneurism of the Innominate Artery and Occlusion of the Left Common Carotid Artery, *Am Heart J* **9** 686, 1933. Cohen, H., and Davie, T. B. Bilateral Obliteration of Radial and Carotid Pulses in Aortic Aneurysm, *Lancet* **1** 852, 1933. Mauer, E. Absence of Pulse in the Vessels of the Upper Extremities and Neck in Aneurysm of the Aortic Arch, *Am Heart J* **17** 716, 1939. Crawford^{18a}. Kampmeier and Neumann^{18b}.

*Data on Twelve Cases of Thrombosis of the Carotid Arteries Without Obstruction of the Subclavian Artery**

Authority and Date	Age of Patient, Years	Sex	Cause	Location of Carotid Thrombus	Condition of Cerebral Arteries	Condition of Brain	Comment
Davy, 1845, cited by Chevers. N. Effects of Obliteration of the Carotid Arteries on the Cerebral Circulation, London M. Gaz 36, 1116, 1845	Middle age	♂	?	Left	Injected and dilated mostly on left side	Softening on left	Sudden right hemiplegia 6 weeks prior to death, dilated aortic arch
Cohn, ¹¹⁴ 1860	66	♂	Embolus?	Left	Thrombosis of middle cerebral artery	Softening on left	Hemiplegia, recovery, stroke and return of hemiplegia 6 months later, with death in 5 days
Fraenkel, ¹¹⁵ 1880	Case 1 50	♂	Aortic aneurysm	Left	Thrombosis of middle cerebral artery	Large softening on left	Right hemiplegia, aphasia, later ocular motor paralysis, death in 3 months
	Case 2 54	♂	Aortic aneurysm	Left	Cerebral vessels not referred to	Softening on left	Transient aphasia, hemiplegia, progressive mental impairment, twitchings of face and extremities
Penzoldt, ¹⁰⁷ 1881	Case 1 50	♂	?	Right (artery apparently arose directly from aortic arch)	Thrombosis of middle cerebral artery	Large softening on right	Sudden diminution of vision later left hemiplegia and hemianesthesia, and epileptiform seizures, death after 1 year
	Case 2 43	♂	?	Left	Thrombosis of middle cerebral artery	Softening on left	Mental disturbances for 1 year, sudden collapse, death after 2 years
Oppenheim, ^{21b} 1891	?	?	Obliterating arteritis	Cervical portion (?), side	?	Softening	Hemiplegia developed slowly
Erb, ^{21c} 1904	50	♂	Aortic aneurysm	Left	Thrombosis of middle and anterior cerebral arteries	Large cyst with porencephaly	Aneurysm, pulseless left common carotid artery, hemiplegia and aphasia for 4 years
Liebhörst, ^{11c} 1907	49	♀	Embolus	Left	Left internal carotid and proximal part of subclavian branches occluded	No softening, less blood on left side	Sudden onset of "cerebral apoplexy", right hemiplegia 4 days prior to death history of "acute endocarditis" with embolic phenomena
Darling and Clark, ¹⁰ 1915	Case 2 34	♂	Syphilitic arteritis	Left (right carotid and right subclavian arteries arose from aorta separately)	Not recorded	Left side slightly smaller	Died of malaria Wassermann test positive, no cerebral symptoms
	Case 3 23	♀	Syphilitic arteritis	Left (arose from innominate artery)	Not recorded	Cyst on left	Died of streptococcal infection Wassermann test positive, no cerebral symptoms
Gladston, Goyons, Worts and others, ^{101d}	Case 1 53	♂	Arterio sclerosis	Left	No cross circulation seen in cerebral arteriogram	Marked cystic changes on left	Sudden right hemiplegia, 2 years, hypertension of "diencephalic type", hyper sensitivity of right carotid sinus
	Case 2 51	♂	Arterio sclerosis	Left	Cross circulation seen in cerebral arteriogram	Hydrocephalus on left	Convulsions since 24 years of age right hemiplegia, 1 year, moderate arterial hypertension, sensitivity of right carotid sinus

* Oppenheim referred to 2 similar cases reported by Trenel and E. Briessaud and de Massary (L'hémiplegie progressive, Rev. Neurol. 6, 570, 1898). He gave only the reference to the work of the latter two. They reported slowly developing right the left Rolandic area, was soft and edematous. Postmortem examination revealed "annular and arteritis" of the carotid artery without thrombosis. The inferior two thirds of hemiplegia in a 19 year old man. Postmortem examination revealed "annular and

Review of the literature (table) brings to light the interesting fact that in 9 of the 11 cases reported, thrombosis of the common and internal carotid arteries occurred on the left side²³ This was also true in our 2 cases In the single case in which thrombosis of the common and internal carotid arteries occurred on the right side, it was associated with a vascular anomaly In 5 of the 11 patients the occlusions were caused by vascular syphilis, in 2 by embolism, in 1, by obliterating arteritis, and in 3 the cause was not discovered Our 2 cases are the only ones that have been reported in which there was associated sclerosis of these arteries Explanation of the predominant sinistral incidence of this condition is far from clear It is known that there is a greater variation as regards the site of origin of the left common carotid artery than the right common carotid artery²⁴ However, developmental anomalies were not relevant in any of the cases Eight of the 11 patients were men, both our patients were men The ages varied from 23 to 66, with an average of 47 years, our 2 patients were 52 and 54 years of age

SUMMARY

The case histories of 2 patients with right hemiplegia and mixed aphasia associated with thrombosis of the carotid arteries of the left side and sensitivity of the carotid sinus reflex of the other side are presented The literature dealing with thrombosis of the carotid arteries is summarized

Thrombosis of the carotid vessels was suspected because of the absence of arterial pulsations The diagnosis was confirmed by study of cerebral arteriograms and encephalograms, surgical exploration and gross and microscopic examination of the specimens

Careful examination of the arteries of the neck in all patients with hemiplegia, convulsive seizures or syncope may lead to more frequent diagnosis of thrombosis of the carotid arteries Often arteriography can be a diagnostic aid

23 In 1 instance the author failed to mention the side involved, the age or the sex of the patient

24 Cunningham, D J Textbook of Anatomy, ed 7, London, Oxford University Press, 1937, p 1166

Progress in Internal Medicine

BLOOD

REVIEW OF RECENT LITERATURE

S MILTON GOLDHAMER, M D

CYRUS C STURGIS, M D

AND

FRANK H BETHELL, M D

ANN ARBOR, MICH

A special effort has been made to consider all of the articles which contribute new information related to the blood and the blood-forming organs. Many of the contributions supplement or confirm present concepts, others offer explanations of certain phenomena which are known to exist. In a review of this nature, in which the available material is so correlated as to be of interest to the reader, many articles may appear unduly stressed, while others of equal merit seem to be overlooked. It is significant to point out also that the number of published articles this year is considerably less, and many of the foreign ones could not be obtained. It is hoped that the omissions which have occurred for one reason or another may be corrected in succeeding reviews.

PERNICIOUS ANEMIA

During the past year, the largest number of articles concerned with this disease have dealt either directly or indirectly with Castle's theory concerning the cause of the anemia of pernicious anemia, which was first elucidated by him in 1929. His interpretation of the role played by the stomach has been subjected to minor criticisms, but in the main it has been sustained. In three papers gastroscopic observations on the mucosa of the stomach are reported. There are several general résumés of knowledge concerning the effect of total gastrectomy in animals in relation to the exhaustion of the erythrocyte-maturing factor in the liver and the production of macrocytic anemia. The puzzling question of the cause of changes in the nervous system still remains unsolved, although some interesting possibilities which have a bearing on etiologic factors have been presented during the past year. Two of the most

From the Thomas Henry Simpson Memorial Institute for Medical Research,
University of Michigan

important papers deal with the demonstrated observation that changes in the cord will not progress provided the patient is adequately treated and with a determination of the time interval before evidence of the disease will recur after treatment is discontinued. Several papers have appeared which confirm the belief, expressed some years ago, that pernicious anemia is a hereditary disease.

Etiology—Heredity. Stamos¹ reviews the previous studies dealing with the role of heredity in pernicious anemia and analyzes the hereditary incidence of anemia among over 600 patients studied at the Simpson Memorial Institute of the University of Michigan. According to the author, there is an increasing tendency in the more recent literature to regard the hereditary influence in pernicious anemia as an important factor in the pathogenesis of the disease. In any study of the familial incidence a number of difficulties confront the observer: (1) errors in diagnosis, (2) difficulty in studying all members of a family, due to their residence in different parts of the country, (3) failure to recognize pernicious anemia as a cause of death in some families, (4) death from accident or incidental disease early in life of members of families, which may affect the statistics, and (5) the possibility that the disease may develop later, even though a member of a family may be in perfect health at the time the study is made, since pernicious anemia tends to occur in the later decades of life. In a study of 645 unselected authenticated cases of pernicious anemia, Stamos found evidence of 51 instances in which there were 1 or more cases in the same family, a familial incidence of 7.9 per cent. In 34 of the 51 families, 1 member other than the patient was found to have the disease, the mother, being affected in 10 instances, the father in 8, the sister in 11 and the brother in 5. Two family histories revealed the presence of pernicious anemia in an uncle and in a paternal aunt, respectively. Five families were represented in which 3 or more of the immediate children had the disease. It is of interest that in a large group of patients with pernicious anemia about 27 per cent stated that there was another case of "anemia" in the family. In a control group of patients without pernicious anemia only 9 per cent made this statement. Stamos believes that the results of this study suggest the importance of a familial hereditary factor in the disease.

Schemm² reports that in 32 cases of pernicious anemia he observed a familial incidence of 18.7 per cent. However, he regards the true familial incidence as higher. Five authenticated cases, those of 4

1 Stamos, H. F. Heredity in Pernicious Anemia, *Am J M Sc* **200** 586, 1940.

2 Schemm, F. R. Pernicious Anemia Family. Five Authenticated Cases in Same Generation, *Am J M Sc* **199** 167, 1940.

brothers and 1 sister, occurring in one family are reported. One additional sister remains in good health, and the only other living member of the family cannot be persuaded to submit to an examination. Two other cases are reported in each of 5 families. Some of the difficulties of studying the hereditary aspect of pernicious anemia are emphasized. For example, it required Schemm five years to accumulate these data, as the patients resided in widely separated points (Philadelphia to Los Angeles).

Askey³ has made a study of cases of "potential" pernicious anemia and suggests a plan of study whereby the disease may be recognized in the latent stage. He considers that the incidence in certain families is such that the genetic factor cannot be questioned. Two hundred and thirty-five instances of multiple familial occurrences were found in the literature, and the disease has been reported in 8 pairs of identical twins, in 4 pairs it appeared in both members, and in 3 it was probably latent in the second member. In the remaining pair, aged 86, although both members had anemia, the second had free acid in the gastric secretions. Furthermore, it has been shown that achlorhydria has an increased incidence in the families of patients with pernicious anemia, reports of many cases have now been collected which indicate that the anacidity precedes the development of the active signs of the disease by many years. Askey considers that persons most likely to have pernicious anemia are those relatives of a patient known to have the disease who show a histamine-refractory anacidity. Bloomfield states that the occurrence of anacidity in a person who has no relative with the disease represents a negligible hazard as regards the risk of later development of pernicious anemia, and he estimates the possibility as 1/300 or 400. There are no data available as a basis for estimating the extra hazard of achlorhydria in relatives of patients with pernicious anemia. Askey studied 20 families in which 2 or more members had pernicious anemia, which makes a total of 235 such families recorded in the literature. This incidence and the occurrence of the disease in monozygotic twins suggest that the disease is frequently, if not invariably, transmitted by heredity. He finds anacidity is twice as high in near relatives as in distant ones. Of the 61 relatives examined, 10, or 16 per cent, were found to have achlorhydria and 4 were considered to have incipient pernicious anemia, as evidenced by macrocytic anemia in 3 and a clearcut history of glossitis and paresthesia relieved by liver therapy in the fourth. Two other relatives had hypochromic anemia. In 2 of the 1 relatives who refused to have a gastric analysis and treatment pernicious anemia subsequently developed, with severe changes in the spinal cord.

3 Askey, J. M. Prevention of Pernicious Anemia. Recognition of Latent Stage in Relatives, *Ann Int Med* **14** 593, 1940.

Askey considers that the development of pernicious anemia and the neurologic complications can be prevented in many instances if all relatives with anacidity are considered as potentially having the disease.

The diagnosis of pernicious anemia in a child is one to arouse suspicion, and Templeton⁴ emphasizes that the disease is rarely encountered in persons younger than 20 years of age. He reports the case of a girl aged 14 and ventures the opinion that she had been suffering from the condition for at least three years. All her life she apparently had been on a deficient diet, especially with respect to protein. According to the author, she "never ate a square meal." Nausea at the sight of most meals was followed by a loose stool and a feeling of distress. For three years there had been periods of moderate pyrexia and extreme weakness. For about a year she had suffered from deep, painful and punched-out buccal ulcers on the tongue, cheeks and lips, and the tongue had begun to appear beefy. A blood count at the time of the latter change showed "a secondary anaemia," with a color index less than 1. About six months later, for the first time, the color index was about 1. The red blood cell count was 2,040,000 per cubic millimeter, the hemoglobin concentration 47 per cent, the white blood cell count 6,400 per cubic millimeter and the color index 1.1. Macrocytosis, microcytosis, poikilocytosis and polychromasia were noted. A fractional test meal showed complete achlorhydria. Full doses of an extract of fresh liver (campolon) and iron had no effect, but 2 cc of purified liver extract (anahaemin) every other day produced a beneficial effect, and in about three months the blood was entirely normal. In our opinion, this patient may have had true Addisonian anemia, but it is difficult to prove from the information which is presented. There is no statement that the patient had achlorhydria after injection of histamine, no data are given about the size of the cells as indicated by the mean corpuscular volume, no neurologic manifestations are mentioned, no data are presented concerning the presence or absence of a reticulocyte response immediately following treatment, and there is nothing to indicate that her condition would not have remained normal if a well balanced diet had been given and the liver extract discontinued. It is impractical, but possible, to ascertain the presence or absence of the so-called intrinsic factor in patients with questionable pernicious anemia. It was not done in this case. The burden of proof is on the one who claims that a child of 14 has pernicious anemia, which means that the diagnosis must be established by all possible means before it can be accepted. A follow-up note on this patient after an interval of several years would be of interest.

Role of the Stomach and the Liver in the Causation of Pernicious Anemia Since Castle's original hypothesis regarding the formation

4 Templeton, W. L. Pernicious Anaemia in Child, *Lancet* 2 1221, 1939

of the erythrocyte-maturing factor was evolved in 1929, new information has come to light, and in the opinion of Formijne⁵ a reconsideration of all available data has become necessary. He has carried out a number of experimental studies which have a bearing on the cause of pernicious anemia and on the mechanism of the normal control of the formation of erythrocytes. The following results were obtained by the author in regard to the extrinsic factor. It was present in a 70 to 80 per cent alcoholic extract of meat, fats and lipoids could be removed from this extract by ether extraction without loss of activity and the extrinsic factor present in the extract passed through an ultrafilter. Less than 50 per cent of the extrinsic factor was present in the precipitate obtained by saturation of the extract with ammonium sulfate. In studying the interaction between the extrinsic and the intrinsic factor *in vitro*, the author concluded

The liver factor [erythrocyte-maturing factor] could not be demonstrated by treatment of the incubated mixture with 70 per cent alcohol and precipitation of the filtrate with 96 per cent alcohol, the precipitate was inactive when given by mouth or by injection.

The conclusion is drawn, contrary to the belief expressed by Wilkinson and his collaborators, that no reaction occurs between the extrinsic and the intrinsic factor *in vitro* and that only an *in vivo* reaction exists.

Geiger, Goodman and Claiborn⁶ state that there are no observations which either have proved a simple storage function of the liver as regards the antianemia, erythrocyte-maturing factor or have excluded the possibility that the active principle is produced by an essential function of the normal liver tissue. In order to test the theory of liver storage of the antianemia principle, stomachs were removed from swine and it was then determined whether the livers of these animals showed a progressive depletion of the effective factor. Totally gastrectomized animals were killed at approximately monthly intervals between the second and the sixth month after operation and also at eighteen and thirty-six months. The livers from these animals were then assayed for the anti-pernicious-anemia principle by administration to patients with pernicious anemia of an extract prepared from them. From the results of these experiments, it is clear that after total gastrectomy in the hog the liver becomes progressively depleted of antianemia potency. An appreciable loss is apparent after the second postoperative month, and the exhaustion is complete after the sixth month. These results con-

5 Formijne, P. Experiments on the Properties of the Extrinsic Factor and on the Reaction of Castle, *Arch. Int. Med.* **66**: 1191 (Dec.) 1940.

6 Geiger, L. S., Goodman, L. S., and Claiborn, L. N. Effects of Gastro-Intestinal Resections in Swine on Antianemia Potency of Liver. Observations on Nature and Sources of Materials Effective in Pernicious Anemia, *Yale J. Biol. & Med.* **13**: 259, 1940.

firm previous reports by these and other authors and suggest strongly that the liver serves merely to store, or to elaborate and store, a product furnished by the stomach. They throw no light on whether the erythrocyte-maturing factor is an interaction product of gastric digestion, a precursor which is further elaborated by the liver cells into the antianemia principle or a hormone originating in the stomach wall. A second series of experiments was designed to determine whether the antianemia principle is a hormone or a product of gastric digestion. One part of this question was answered by an ingenious experiment in which the continuity of the stomach with the gastrointestinal tract in swine was severed completely at both the cardiac and the pyloric end, while as much as possible of the gastric nerve and blood supply was preserved. Under such conditions, according to the theory of Castle, the interaction between the extrinsic food factor and the intrinsic gastric factor would be disturbed and the liver would suffer loss of potency, precisely as after gastrectomy. The animal on which such an operative procedure had been carried out was killed in the eighth postoperative month. Assay of this liver on 2 patients with pernicious anemia indicated that it did not contain the anti-pernicious-anemia principle. It appears, therefore, that the digestive role of the stomach is essential to the formation of the erythrocyte-maturing factor present in liver. Results of further experiments indicated that the liver of the newborn pig has some reticulocytogenic effect, although apparently less than is found in normal adult hog liver, and that the livers of fetuses obtained from an agastric sow are lacking in this principle. These observations tend to corroborate those on the isolated stomach preparation, and the two together imply that gastric digestion is essential for the production of the antianemia principle. Another experiment was done to determine if the duodenum of the hog was a significant source of the anti-pernicious-anemia factor. The proximal 15 feet (457 cm.) of intestine was removed from a hog and the stomach left intact. The animal was killed eight months later. Assay of the liver from this animal showed an appreciable decrease in the antianemia principle. Thus it appears that the duodenum is a true and significant source of the intrinsic factor, but that it is relatively less important than the stomach in this respect.

An attempt was made to produce pernicious anemia in swine by extirpating all known sources of the intrinsic factor, namely, the stomach and the duodenum. In 2 pigs the entire stomach and 15 to 20 feet (457 to 609 cm.) of the proximal portion of the intestinal tract was removed. Assays of the livers of the 2 animals at the end of six weeks and four months, respectively, showed that extirpation of both the stomach and the duodenum exhausts the liver of antianemia principle more quickly than does the removal of either organ alone. Observations

on changes in the bone marrow, the blood and the nervous system are to be published at a later date. The authors conclude from these experiments that the liver stores, or elaborates and stores, a product furnished by the stomach. As the liver is depleted in the isolated stomach preparation, it is suggested that the effective factor results from gastric digestion rather than from an internal secretion of the stomach. The fact that livers of newborn pigs from a normal sow contain the active principle and that the livers of the newborn pigs from an agastric sow do not also suggests that the active factor is a product of gastric digestion. Results of additional experiments indicate that the duodenum, as well as the stomach, is a true source of the intrinsic factor. Because these authors have contributed new and important information bearing on the cause of pernicious anemia, their paper deserves the careful perusal of all those who are interested in the disease.

Relation of Gastrectomy to Pernicious Anemia. It is considered by Ivy⁷ that the functions of the stomach are those of (1) a reservoir and (2) of a triturating, (3) digestive, (4) hematopoietic, (5) bacteriostatic and bactericidal and (6) coabsorptive organ. He believes that observations on gastrectomized animals indicate that the stomach cannot be considered as an essential organ in a strict sense. Since 1923 attempts have been made in Ivy's laboratory to produce the blood and bone marrow picture of pernicious anemia in animals by gastrectomy and dietary modification. All attempts have met with failure, and the author has no faith in the few reports to the contrary which appear in the literature. He believes that the differences observed between the reaction to gastrectomy of the rat and the pig, on the one hand, and that of the dog and the monkey, on the other, in regard to anemia may be due to a true "species difference." He suspects, however, that the difference is more likely attributable to "the degree of success that has been attained in the search for an adequate diet" following gastrectomy. With the diet he has employed after gastrectomy changes have not occurred in the mouth, tongue, skin or nervous system. An important point is stressed, as follows:

Obviously the presence of diarrhea or mushy stools, especially if associated with rapid intestinal passage, will predispose to mineral, vitamin and protein loss, all of which are concerned in the genesis of the various disturbances observed in gastrectomized animals.

It is concluded that total gastrectomy does not cause pernicious anemia, combined degeneration of the spinal cord, stomatitis and glossitis in the rat (after one year), dog (after twelve years), pig (after three years) or monkey (after two and six-tenths years).

⁷ Ivy, A. C. Effects of Gastrectomy in Animals, *Am J Digest Dis* 7:500 1940

Bussabaiger, Ivy, Wigodsky and Gunn⁸ were led to investigate the effects of gastrectomy in the monkey because they realized that until pernicious anemia can be produced experimentally its cause will probably remain uncertain. From Castle's studies they concluded that the complete removal of the stomach from animals should provide valuable corroborative data relating to his hypothesis. After observations on the blood of 8 monkeys were recorded for one month under normal conditions, the stomach was removed and the lower end of the esophagus anastomosed to the duodenum. Two of the animals succumbed within a period of three weeks after the operation. One died of tuberculosis one hundred and eighty-seven days after the operation. The remaining 5 survived four hundred and seventy-eight to nine hundred and thirty-seven days, and they would have lived longer if it had not been for certain experiments. In none of them did there develop the blood picture of pernicious anemia as seen in man. This work confirms that of Goldhamer, who reported that gastrectomy in the monkey is followed after six months not by the blood picture of pernicious anemia but by that of anemia with a low color index. These observers can say further that such a blood picture did not appear within approximately three years. Sometimes the hypochromic anemia which was observed responded to the administration of ferric citrate and liver extract, but at other times it did not. In some instances it disappeared spontaneously. One monkey, whose pregnancy was first diagnosed seven hundred and sixteen days after gastrectomy, delivered a full time fetus. Although this animal did not have anemia during pregnancy, the condition occurred during the puerperium, with a red blood cell count as low as 3,740,000 per cubic millimeter. Two gastrectomized monkeys and 1 normal animal were fed a diet devised by Wills, similar to that of Mohammedan women in Bombay, who frequently have macrocytic anemia. None of the animals survived on this diet more than one hundred and fifty-two days, but at the time of death none had macrocytic anemia. The bone marrow of a gastrectomized monkey fed such a diet showed a great proliferation of undifferentiated cells (hemocytoblasts) and an excessive quantity of pigment. These changes were not reflected in the circulating blood. A comprehensive discussion of the cause of pernicious anemia, with especial reference to the gastric factor, is presented, and a complete bibliography is given.

The establishment of the fact that the stomach secretes the intrinsic factor which is concerned with the development of the red blood cells and with the causation of pernicious anemia makes gastrectomy, complete or partial, a procedure which must be considered from these

⁸ Bussabarger, R. A., Ivy, A. C., Wigodsky, H. S., and Gunn, F. D. Effect of Gastrectomy on Monkey, *Ann Int Med* 13 1028, 1939.

standpoints, according to Jones.⁹ A careful review is given of the investigations dealing with the relation of the stomach to the anemias and with the effects of gastrectomy. The author concluded that a major gastric operation, such as either total or subtotal gastrectomy, may be performed without any great concern or undue consequence as far as interference with normal hematopoiesis is concerned. Regardless of the fact that relative or absolute achlorhydria may result and the secretory cells of importance to normal physiologic activities of the blood may be removed, the development of serious anemia need not be feared. It is admitted that occasionally severe microcytic or macrocytic anemia may follow an extensive operation on the stomach, but in all probability it can be readily controlled with iron and/or liver therapy. The author concludes with this statement:

The search for the exact site of formation of the intrinsic antianemic factor must still be pursued, but in spite of our lack of accurate knowledge as to its source, proper gastric surgery need not be avoided.

Gastroscopic Observations in Patients with Pernicious Anemia
According to Schindler and associates,¹⁰ atrophic gastritis is found constantly in cases of pernicious anemia, sprue and combined degeneration of the cord and in many cases of gastric carcinoma, in which it apparently precedes the development of the tumor. It is also claimed that atrophic gastritis, without associated disease, may occur. This appears to be a primary disease entity of unknown etiology. A number of investigators have observed that the gastric mucosa will regenerate completely after liver therapy in cases of atrophic gastritis associated with pernicious anemia. It has also been noted by others, and confirmed, that a similar regeneration of atrophic mucosa will occur in cases of atrophic gastritis without pernicious anemia after liver therapy. It has been suggested that in some cases atrophic gastritis may be the result of a lack of the antianemia factor without associated changes in the blood and also that a parallelism between atrophy of the tongue, of the pharynx and of the stomach and changes in the cord should be assumed. Furthermore, it has been found that in some cases of hypochromic anemia the atrophy of the mucosa has disappeared after iron therapy. According to Schindler, Kirsner and Palmer, the evidence seems to indicate that in some cases, at least, atrophic gastritis is related to a deficiency state. There is no available information to indicate that

9 Jones, C. M. Problem of Gastrectomy and the Anemias, *Am J Digest Dis* 7 502, 1940.

10 Schindler, R., Kirsner, J. B., and Palmer, W. L. Atrophic Gastritis. Gastroscopic Studies on the Effects of Liver and Iron Therapy, *Arch Int Med* 65 78 (Jan) 1940. Schindler, R., Nutter, P. B., Groom, H. E., and Palmer, W. L. Anatomic Foundation of Anacidity. Gastroscopic Study, *ibid* 66 1060 (Nov) 1940.

the improvement in the gastric mucosa is a true histologic regeneration, for microscopic studies are not available. The fact remains, however, that the living mucosa, in cases in which there has been a response to treatment, cannot be distinguished from a normal mucosa. This observation led Schindler and his associates to employ systematic substitution therapy in 8 cases of atrophic gastritis not associated with pernicious anemia, sprue, combined degeneration of the cord or pellagra. They found that in some, but not all, of the cases liver therapy or liver and iron therapy caused the mucosa to appear normal again. It is impossible, in their opinion, to state whether the regeneration is genuine, that is, whether it is due to the formation of new glands, as microscopic examinations are necessary to settle this question. The use of liver, iron or vitamins is justified in the treatment of atrophic gastritis, according to them, but it is emphasized that additional careful studies are necessary in order to evaluate such therapy.

According to Miller,¹¹ the modern view concerning gastritis is that "the clinical diagnosis is justified only as a result of gastroscopic observation, though such a study at best gives one only a visual picture of the gastric mucosa." Attempts at more exact studies may be misleading, as specimens of the stomach made available by operation or necropsy are so altered that they may give erroneous information. Miller does not believe that the type of gastritis can be classified. He prefers merely to describe his observations. A brief résumé of the literature bearing on the relation between changes in the stomach and pernicious anemia is given. After reference to the older literature, he considers the work of Faber and of Huist, who both claimed that the achlorhydria of pernicious anemia is to be explained on the basis of a gastritis. Faber expressed the belief that the gastritis produces changes in the pyloric region which bring about a suppression of the intrinsic factor and therefore is the cause of pernicious anemia. On the other hand, Meulengracht found in 8 cases of pernicious anemia that the maximal gastric alterations occurred in the fundus. They were of an atrophic nature, with disappearance of both the chief and the parietal cells. This would explain the achylia gastrica but would not account for the absence of the intrinsic factor, which is secreted mainly in the pyloric region. These observations were substantiated by those of Magnus and Ungley. The latter expressed the opinion that the fundal atrophy results perhaps from some endocrine, nutritional or congenital factor, rather than from an inflammatory change. The observations of gastroscopists indicate that the gastritis in most cases of pernicious anemia is of the atrophic type, but sometimes it is said to be hypertrophic. Both degenerative and

11 Miller, T. G. The Relation of Gastritis to Anemias, *Internat. Clin.* **1** 173, 1940.

inflammatory lesions have been noted, involving on some occasions the entire mucosa and at other times only that of the fundus or the antrum. The additional evidence of the freedom of the antrum from involvement in some cases suggests that antral gastritis is not, as Faber suggested, the explanation for lack of the intrinsic factor. Furthermore, some observers have reported regeneration of the mucosa after treatment with liver. This statement has been questioned. Recent investigations have suggested that the gastric secretion in patients with pernicious anemia contains a substance, not present in normal persons or in those with cancer of the stomach, which causes suppression of the secretion of hydrochloric acid. If this is true, then the gastritis, even though it is present, may not be the cause of the achlorhydria. According to Schindler's theory of the relation of the stomach to pernicious anemia, absence of an antianemia substance may produce atrophic gastritis before it causes the anemia. He stated the opinion that in pernicious anemia some factor is lacking and that this lack is responsible for the syndrome, including the inflammation and atrophy of the tongue, the pharynx, the stomach and the intestine as well as the anemia and the neural manifestations. Schindler expressed the belief also, according to Miller, that in pernicious anemia two separate conditions are present in the stomach, primarily, a dysfunction of the cells that produce the intrinsic factor and, secondarily, degeneration or atrophy of the surface epithelium. With the atrophy, he suggested that there may be superimposed inflammatory changes. In conclusion, Miller states that a review of the literature suggests that chronic gastritis, usually of the atrophic type, is commonly associated with pernicious anemia and sometimes with other forms of anemia and that it frequently precedes the alterations in the blood in Addisonian anemia, but that at the same time certain recent data and opinions lead one to doubt that gastritis is the cause of pernicious anemia. He considers that there is no definitely established etiologic relationship between the two diseases.

Carey¹² states that gastroscopic examination of the stomach in patients with pernicious anemia has demonstrated the presence of atrophy of a greater or less degree. Whether or not the gastric mucosa returns to normal in patients who have been treated with liver is a matter about which all observers are not in accord. The author has never seen a patient with pernicious anemia who had a normal gastric mucosa, and, moreover, he has not observed restoration of gastric mucosa to normal in any patient examined after treatment. In some there has been evidence of regeneration. After a study of 15 cases of pernicious anemia by means of the gastroscope, he concluded that this regeneration is not

12 Carey, J. B. Gastroscopic Observations in Pernicious Anemia, *Minnesota Med* 23 311, 1940

evidence of a return to complete normality, which would imply that the glands could again secrete hydrochloric acid and the intrinsic factor would return, neither of which processes recurs. He believes that the gastric mucosa might show gross evidence of improvement in color and even in the direction of recession of the atrophic characteristics. This is probably due to improvement in the general condition and in the blood brought about by the anti-pernicious-anemia therapy.

Relation of the Gastric Secretions to Pernicious Anemia It has been previously shown by Taylor and his co-workers that normal gastric juice contains a proteolytic enzyme capable of hydrolyzing casein to the proteose stage in an alkaline medium, but not at hydrogen ion concentrations below 4.0. This would appear to distinguish the enzyme from pepsin, while the failure of the enzyme to produce large amounts of amino nitrogen within twenty-four hours also eliminates trypsin and erepsin. Although it cannot be proved that the proteolytic activity is identical with that of the intrinsic factor, it is of interest to note that such activity is retained or destroyed under certain circumstances which affect the clinical potency of the intrinsic factor in a similar fashion. The present publication of Gessler, Dexter, Adams and Taylor¹³ is an attempt to demonstrate further resemblances of this nature. They show that the agent which is responsible for the proteolytic activity in vitro of normal human gastric juice at a p_H of 7.4 may be completely removed by adsorption with Lloyd's reagent. In this respect it resembles the so-called intrinsic factor. It has also been demonstrated that this enzyme is unable to penetrate a semipermeable membrane. Furthermore, it was found in this study that because of the usual presence of interfering enzymes from the intestine, the in vitro method was unsatisfactory for determining in cases of pernicious anemia the amount of proteolysis which could be ascribed to the proteolytic agent in normal human gastric juice.

Schenken, Stasney and Hall¹⁴ agree with the generally accepted theory that the active anti-pernicious-anemia principle is formed by an interaction of a substance secreted by the stomach with some material in the food and that the active principle thus formed is stored in the liver. Considerable controversy has arisen, however, concerning the production and nature of this substance. It was thought that information which would have a bearing on these questions might be gained

13 Gessler, C. J., Dexter, S. O., Adams, M. A., and Taylor, F. H. L. Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia. VIII. Further Studies of the Proteolytic Activity of Normal Human Gastric Juice in Vitro, and the Limitations of the Method in Pernicious Anemia, *J. Clin. Investigation* **19**: 225, 1940.

14 Schenken, J. R., Stasney, J., and Hall, W. K. Antianemic Principle in Human Liver in Carcinomas of Stomach and Cecum, *Am. J. M. Sc.* **200**: 11, 1940.

if tests were made of the antianemia potency of the livers of patients with carcinomas which had destroyed various portions of the gastrointestinal tract. The results were as follows. The liver of a patient with scirrhous carcinoma of the pars pylorica did not contain the active principle, as indicated by its failure to produce the anticipated response when a liver extract prepared from it was administered to a patient with typical Addisonian pernicious anemia in relapse. On the other hand, an extract prepared from the liver of a patient whose death was due to gastric carcinoma which involved the entire stomach, except a portion of the pars pylorica, did contain the active principle. The administration of extracts prepared from the livers of the 2 patients with carcinoma of the stomach to another patient with typical Addisonian pernicious anemia in relapse confirmed the observations just described. The hematopoietic principle was present in an extract of the liver of a strikingly emaciated patient who died with carcinoma of the cecum. As it is considered that the most active part of the gastric mucosa in the production of the active principle is the pyloric region, it seems significant that the antianemia principle was found to be absent in the patient who had carcinoma involving the pyloric mucosa and that it was present in the liver of the patient whose entire stomach, except for the pylorus, was involved by the carcinoma.

Morrison¹⁵ believes that the anti-pernicious-anemia potency of the stomach may be attributed to the fundus region, as well as to the other portions, and that this activity is ordinarily neutralized by the action of pepsin, a product primarily of the fundus. Greenspon, several years ago, advanced the theory that an extrinsic factor, as conceived by Castle, was necessary for the formation of an antianemia principle only as a protection from the inactivating effect of pepsin and that the intrinsic factor was the sole essential element. Greenspon's contention, if confirmed, would strongly support that of Morrison. The latter's studies have shown that the feeding of depepsinized whole stomach mucosa, with and without the addition of extrinsic factor, was not "significantly" effective in cases of pernicious anemia and that the feeding of depepsinized pyloric mucosa without the extrinsic factor was ineffective, when extrinsic factor was added to this, however, there was definite, but minimal, evidence of anti-pernicious-anemia activity. Greenspon's claim of higher activity by depepsinization has not been sustained, nor has his concept of the existence of an anti-pernicious-anemia principle, excluding the action of the extrinsic factor, been confirmed. Morrison suggested that it may not be possible to depepsinize fundus tissue completely and that this failure may account for the inactivity of fundus preparations. Morrison believes that the fundus may play a role in pernicious anemia.

15 Morrison, S. Studies in Pernicious Anemia. Inquiry into Role of Pepsin, *Ann Int Med* 14 242, 1940.

This is suggested by (1) Greenspon's demonstration, unless disproved, of the antagonism of pepsin toward the anti-pernicious-anemia factor of Castle, (2) the known adsorptive capacity of protein for pepsin and (3) predominance of the peptic cells in the fundus. We do not necessarily agree with the reason which Morrison has advanced for the importance of the fundic glands in pernicious anemia, but attention is directed to the recent observation that it is atrophy of these glands, rather than of those in the pylorus, which is found in patients who succumb to pernicious anemia.

Bloomfield has previously made observations which indicate that the gastric secretion decreases with advancing years. This finding, however, was based on averages of many examinations on different persons, and no information was available as to what happens in the individual patient. In an attempt to answer this question, he previously reported the results of standard histamine tests repeated on the same persons after an interval of five years. Apparently, the five year period was too brief for conclusive results. Recently it was possible to reexamine 5 essentially normal people whose gastric secretions had been studied ten years previously. It was found¹⁶ that after this interval some persons show little or no change, whereas in others there is a definite diminution. Three of the 5 showed practically identical secretions, 1 had a slight decline of acidity but not of volume, and in 1 there was a definite decrease of both volume and acid. According to the author, it is not known why some preserve their secretion unaltered over many years and others show a rapid decline. It had previously been demonstrated by Goldhamer¹⁷ that pernicious anemia is associated not with an absence of the intrinsic factor but with a diminished amount, which may be proportional to the total volume of the gastric secretions. Since the volume may diminish with age in some persons, this relationship may be one of the factors which accounts for the greater incidence of pernicious anemia in older people.

In a discussion of Meulengracht's statement, in 1935, that atrophy of that part of the stomach which comprises the "pyloric-gland region" resulted in lack or diminution of the intrinsic factor, Weber referred to a case which he and Huber¹⁸ now report complete in all details. At the time of the discussion, the case was considered to be one of pernicious anemia, possibly due to atrophy of Meulengracht's "pyloric-gland region," although the fundic glands were still able to secrete

16 Bloomfield, A. L. The Decrease of Gastric Secretion with Advancing Years. Further Observations, *J. Clin. Investigation* **19** 61, 1940.

17 Goldhamer, S. M. The Presence of the Intrinsic Factor of Castle in the Gastric Juice of Patients with Pernicious Anemia, *Am. J. M. Sc.* **191** 405, 1936.

18 Weber, F. P., and Huber, H. Megalocytic Anemia in a Case of Jejunal Ulcer with Fatal Perforation, *Acta med. Scandinav.* **104** 543, 1940.

sufficient quantities of hydrochloric acid and of pepsin. The patient's condition had been classified as pernicious anemia without achlorhydria, but after the necropsy it was conceded that he could not be regarded as having suffered from true pernicious (addisonian) anemia in the modern sense of the term. The blood picture was typical of pernicious anemia, hydrochloric acid was present in the gastric secretions, and a response to liver therapy occurred. At necropsy a perforating jejunal ulcer was found.

Dr Witts regards this case as one of megalocytic anemia secondary to jejunal ulceration, similar to numerous other cases of megalocytic anemia with associated intestinal stenosis. The authors quote Dr L J Witts as follows:

Before diagnosing pernicious anemia with normochlorhydria, I should demand complete exclusion of any pathological lesion in the alimentary tract, and also proof of the diagnosis by the Price-Jones curve, sternal puncture and stool analysis.

Sandorf and Davidhoff¹⁹ propose that the terms pernicious and allied anemias be discarded and the designation gastric anemia be substituted. Furthermore, they would replace the name pernicious anemia with the term achylia gastric anemia and for hypochromic, commonly called secondary, anemia they would employ the term hypochlorhydric anemia. They maintain that this type of nomenclature places the proper emphasis on the functional derangement of the gastrointestinal tract in such anemias and therefore is more intelligible. We are in accord with their concluding statement, namely:

The relationship between the function of the gastro-intestinal system and the state of the hematopoietic system should receive due recognition in both therapy and nomenclature.

Cause of the Changes in the Nervous System Occurring in Pernicious Anemia—Wintrobe, Miller and Lisco²⁰ have continued their studies on the relation of the diet to the occurrence of ataxia and degeneration in the nervous system of pigs. Previously they had observed certain neural changes in growing pigs fed a simplified diet, deficient in vitamins. Further studies have shown that the deficient substance is not vitamin A, thiamine, riboflavin, or nicotinic acid and is probably not vitamin E. Neither inanition nor mineral deficiency appears to be concerned in the production of the lesions. Their experiments were carried out as follows: Forty-four pigs, with an average age of 3 weeks,

19 Sandorf, M., and Davidhoff, M. Gastric Anemia Syndromes, J. Indiana M. A. **33** 523, 1940.

20 Wintrobe, M. M., Miller, L. J., Jr., and Lisco, H. The Relation of Diet to the Occurrence of Ataxia and Degeneration in the Nervous System of Pigs, Bull. Johns Hopkins Hosp. **67**:377, 1940.

were raised on a basal diet containing casein, sugar, lard, a mineral mixture, cod liver oil, ascorbic acid and varying amounts of yeast. When the yeast intake was eliminated or reduced to a low level, despite an adequate amount of thiamine, riboflavin or nicotinic acid in the diet, a condition developed which was characterized by ataxia and extensive lesions in the nervous system. These lesions consisted of degenerative changes in the peripheral nerves, the spinal ganglions, the posterior roots and the dorsal funiculi of the spinal cord. In extreme degrees of change there were also lesions of the anterior horn cells. When a filtrate factor obtained from yeast was added to the diet, less extensive changes occurred, but even when whole dried yeast was furnished in large amounts, only 5 of 12 pigs remained free from the lesions. In none of the pigs fed whole desiccated liver did changes referable to the nervous system develop. Wheat germ oil failed to prevent the neural lesions. These carefully controlled experiments are of interest for many reasons, but especially from the standpoint of the cause of the neurologic changes in pernicious anemia. They have demonstrated that a striking degenerative type of lesion of the nervous system can be produced in pigs by a dietary deficiency. While there is not general agreement concerning the cause of the changes in the spinal cord and the peripheral nerves occurring in pernicious anemia, the most likely possibility at present is the lack of some component in the diet or the inability to absorb or utilize it.

Field and associates²¹ have made the interesting suggestion that the neural changes in pernicious anemia may be due to a thiamine deficiency. The lack occurs not necessarily because the dietary intake of this substance is low but because subjects with achlorhydria require a larger intake of the material than do those with normal gastric acidity. This increased demand is attributed to a phenomenon observed by him and his collaborators,²² namely, that thiamine is destroyed in bile and pancreatic juice when these secretions are unmodified by the acid in the stomach.

Miscellaneous Clinical Observations in Cases of Pernicious Anemia — Layne and Boyden²³ have conducted a series of studies dealing with the mechanism of emptying the gallbladder. In the first group of patients observed, it was noted that those with peptic ulcer displayed a significantly faster rate of emptying than did controls of a comparable age. This increased rate was attributed to a greater food stimulus, rather than

21 Field, H, Jr, Robinson, W D, and Melnick, D. Vitamins in Peptic Ulcer, *Ann Int Med* **14** 588, 1940.

22 Robinson, W D, Melnick, D, and Field, H, Jr. Urinary Excretion of Thiamin in Clinical Cases and the Value of Such Analyses in the Diagnosis of Thiamin Deficiency, *J Clin Investigation* **19** 399, 1940.

23 Layne, J A, and Boyden, E A. Evacuation of the Gall Bladder in Patients with Pernicious Anemia, *Proc Soc Exper Biol & Med* **43** 534, 1940.

to an increased production of gastric juice. This interpretation was supported by observations on patients with carcinoma of the stomach, in whom it was found that a striking reduction of the amount of free hydrochloric acid failed to retard the emptying of the gallbladder. The present report is based on a study of 22 patients with pernicious anemia who were treated with liver extract. The hemoglobin of the blood either had reached normal levels or was responding to treatment. The histamine test disclosed complete absence of free acid in all patients and only minimal amounts of total acids. Of special interest was the fact that the gallbladder could be visualized in only 60 per cent of these patients, notwithstanding the use of the intravenous method of introducing the dye and the absence of any history of disease of the gallbladder. Visualization failed in only 9 per cent of the patients with ulcer and in 22.7 per cent of those with carcinoma. For the remaining 13 of the 22 patients in whom the gallbladder could be visualized, the mean curve of emptying of the gallbladder approximated that for the controls. Since there was complete absence of free hydrochloric acid in all 22 patients, even after stimulation with histamine, it must be concluded that free hydrochloric acid in the stomach is not essential in the evacuation of the human gallbladder.

Vannotti²⁴ reports 2 cases of pernicious anemia in which he considers that myxedema was a complication. This is an association which we have observed occasionally, but which we have thought, in all probability, existed on the basis of an incidental association. Vannotti, however, believes that there is an etiologic relationship between the two conditions. He speculates that as the iron content of the blood and tissues is elevated in cases of pernicious anemia, the tissue metabolism is stimulated. This metabolic increase, he assumes, acts on the cells of the thyroid gland, and their normal stimulus is put at rest. As a result, he concludes, myxedema might develop in some cases. To us, such a highly theoretic explanation of this association seems hardly necessary.

It is stated by Szekely²⁵ that anemia is occasionally associated with cardiovascular disturbances, especially with functional cardiac signs and symptoms and with angina pectoris, but there is still a wide diversity of opinion as to the frequency with which it occurs. A complete review is given of the literature dealing with the subject. Electrocardiographic studies were made in 76 selected cases of anemia in which clinical examination did not reveal any signs of disturbances of the cardiovascular system or any extracardiac conditions that might also produce electro-

24 Vannotti, A. Anémie de Biermer et hypothyroïdisme, *Schweiz med Wchnschr* **16** 1106, 1940.

25 Szekely, P. Electrocardiographic Findings in Anaemia, *Brit Heart J* **2** 1, 1940.

cardiographic changes The material consisted of 32 cases of pernicious anemia and 44 cases of secondary anemia of the hypochromic type It is emphasized that in the cases of pernicious anemia the patients were aged and slight sclerotic changes in the coronary arteries could not with certainty be excluded, in spite of normal clinical findings Of the 76 selected cases of the two different types of anemia, electrocardiographic changes were found in 23 Most frequently flattening of the T wave occurred, less frequently depression of the S-T segment and low voltage were observed A case of hypochromic anemia was reported in which inversion of the T wave in leads II and III occurred after a profuse hematemesis The electrocardiographic changes entirely disappeared at an early stage, when only slight improvement of the anemia had been observed The author concludes that there is not always a close parallelism between the cardiac changes and the degree of anemia It appears to him that in acute and chronic anemia, angina pectoris or electrocardiographic changes are not merely due to the anemia causing anoxemia of the heart muscle, but in some cases to reflex vasomotor change as well In chronic anemia, the primary myocardial anoxemia as the direct result of the diminution of the oxygen-carrying power of the blood may play a more decisive role But besides this factor, toxic influences must be taken into consideration, as they may affect the myocardium directly

Erf and Rhoads²⁶ recall that the absorption of sugar and fat in patients with sprue is improved after treatment with liver extract and that patients with pernicious anemia with a diminished rate of absorption of dextrose become normal after similar therapy Basing their conclusion on these two observations, the authors state that there is a dysfunction of the intestinal tract which may be corrected by some constituent of liver extract The malabsorption of dextrose and fat cannot be utilized as evidence that liver extract is absorbed imperfectly in the two diseases, for the active principle is probably a breakdown product of protein, most likely a peptide For this reason the authors have studied the absorption of aminoacetic acid by patients with sprue or pernicious anemia, as well by those with other disorders Their observations with the aminoacetic acid tolerance test on patients with sprue or pernicious anemia suggest that this substance is absorbed from the gastrointestinal tract in patients with pernicious anemia more slowly than in normal persons Evidence of this abnormality was not found in the same patients after the administration of liver extract, nor was malabsorption found in patients with intractable diarrhea, severe refractory anemia or pernicious anemia in complete or partial remission, but it was present in 2 patients with cirrhosis of the liver Since no patient with sprue or

²⁶ Erf, L. A., and Rhoads, C. P. Glycine Tolerance Test in Sprue and Pernicious Anemia, *J. Clin. Investigation* **19** 409, 1940

untreated pernicious anemia presented evidence of abnormally increased deamination and since no aminoacetic acid was lost from the bowel during the test, it is assumed that the flat curve for plasma amino nitrogen, observed in such patients, indicated that the absorption of aminoacetic acid was impaired. The authors conclude that the abnormalities in handling aminoacetic acid may be due to a lack of some constituent of liver extract which is not the anti-pernicious-anemia substance.

Goodall²⁷ comments that, obviously, childbirth cannot be common among patients with pernicious anemia, for the incidence of the disease is comparatively low until after the child-bearing age. He reports the case of a patient who was first seen in 1930, at which time she was 34 years of age. She then had the fully developed blood picture of pernicious anemia, with a red cell count of 1,500,000 per cubic millimeter and a hemoglobin concentration of 31 per cent. She was treated efficiently with various stomach and liver preparations. In 1938 she became pregnant and was delivered in January 1939. At the time of delivery the red blood cell count was 4,200,000 per cubic millimeter and the hemoglobin concentration 60 per cent. Because of retained placenta considerable blood must have been lost, for the patient went into shock and required blood transfusions. A day or so after delivery the red blood cell count was 1,900,000 per cubic millimeter and the hemoglobin concentration 48 per cent. Approximately nine months later the concentration of hemoglobin was 94 per cent.

Bigg²⁸ made a study of the size of the spleen in patients with pernicious anemia, as there seemed to be some difference of opinion regarding this question. Some authors stated that the spleen is palpable in 20 to 40 per cent of cases. Others reported that it is rarely enlarged. It was found to be palpable in only 3 per cent of the 200 consecutive patients with pernicious anemia examined at the Simpson Memorial Institute of the University of Michigan. In 18 of these patients on whom necropsies were performed the weight of the spleen varied from 95 to 640 Gm, the average being 265 Gm. In 17 of the 18, the spleen was larger than the commonly accepted normal weight of 150 Gm. A necropsy was done on only 1 of the patients with splenomegaly for whom the clinical diagnosis of pernicious anemia was made. This patient was found to have cirrhosis of the liver. Although the spleen in cases of pernicious anemia is usually observed to be enlarged at necropsy, it is rarely increased to the size which makes it palpable during life, as it may be increased 400 per cent and still not be felt on physical examination.

27 Goodall, A. Successful Pregnancy in Old-Standing Pernicious Anaemia, *Lancet* **1**:30, 1940.

28 Bigg, E. Spleen Size in Pernicious Anemia, *Ann Int Med* **14** 277, 1940.

The Active Principle and Treatment of Pernicious Anemia—Test for Potency After reviewing the various laboratory tests for estimating the potency of various anti-pernicious-anemia preparations, Schlicke²⁹ concludes that they do not yield uniform or satisfactory results. A recent approach has been an attempt to influence the rate of maturation of the blood of the developing fetus, as the similarity has been pointed out between the changes which occur in the blood of a developing fetus and those which are present in the blood of an adequately treated patient with pernicious anemia. Schlicke states that if it could be demonstrated that fetal hemopoiesis can be accelerated by administration of antianemia preparations, a test of great practical importance might be available. Studies by this observer indicate that normal human gastric juice contains a substance which when administered orally to pregnant albino rats produces in the blood of a fetus a significant increase in the number of circulating erythrocytes and a decrease in their volume and diameter which can be detected at birth. This substance has no effect on the number of reticulocytes or nucleated red cells in the blood of the fetus. Its activity is enhanced by neutralization and destroyed by heating; it is claimed to be absent from the gastric juice of patients having pernicious anemia. Its presence is demonstrable in variable amounts in the gastric juice of patients with simple achlorhydria or with carcinoma of the stomach. This substance has not been identified as the intrinsic factor, nor has it been established that it accelerates maturation, although the author suggests that the increase in the number of red blood cells and a decrease in their volume and diameter might be explained as the result of the premature appearance of later generations of erythrocytes, presumably from the fetal bone marrow which has been subjected to stimulation. Thus, the author admits, is actually maturation in the broader sense.

Active Principle in Urine As the normal human urine, according to Wakerlin,³⁰ contains a substance which is reticulocytogenic for the pigeon, rat and guinea pig and is said to be effective in the treatment of pernicious anemia, consideration was given to the possibility that the reticulocytogenic principle in urine and the hemopoietic principle in liver might be similar. This is also suggested by the observation that kidney is effective in the treatment of pernicious anemia. For this reason, the reticulocytogenic substance from normal human urine was administered orally and intramuscularly to patients with pernicious anemia. The results demonstrated conclusively that the anti-pernicious-anemia principle in liver is not excreted in significant quantities, if at all, in normal

29 Schlicke, C. P. Blood of Newborn Rats After Oral Administration to Mother of Normal and Abnormal Gastric Juice, *Am J M Sc* **200** 155, 1940.

30 Wakerlin, G. E. Effect of Reticulocytogenic Principle in Urine in Treatment of Pernicious Anemia, *Arch Int Med* **65** 21 (Jan) 1940.

human urine It is also concluded that the principle in kidney which is effective when given by mouth to patients with pernicious anemia is reticulocytogenic for the pigeon but is ineffective when administered intramuscularly to patients with pernicious anemia

Method of Assay by Increase in Red Blood Cells The standard reticulocyte equations have been of value in estimating the clinical effectiveness of various agents in treatment of pernicious anemia, but their accuracy has been questioned by some observers It is held by some that the increased number of reticulocytes present after treatment serves qualitatively to indicate the presence of active material in the substance used for treatment, but such an increase cannot be employed as a quantitative measure of the amount of effective material administered This opinion is based on the apparent lack of correlation between the amount of active liver principle given and the magnitude of the reticulocyte response, on the one hand, and the extent of the erythrocyte increase, on the other It is stated by Riddle³¹ that the rise in the erythrocyte count in response to therapy would be a far simpler criterion for evaluating the effect of treatment than the reticulocyte response if the expected erythrocyte increase were expressed in as simple and as accurate a form as the standard reticulocyte equations The study by Riddle is an analysis of the quantitative relationships existing in 600 patients with pernicious anemia between the erythrocyte counts before treatment and the increase in the erythrocytes after treatment He concludes that the average weekly increase in the erythrocyte count at the end of two weeks of treatment had an inverse relationship to the erythrocyte level before treatment This may be expressed in the form of an equation, which he suggests be used as a standard for the effectiveness of treatment as follows $I = 0.78 - 0.174E_0$, in which I is the average weekly increase in the erythrocyte count after two weeks of treatment and E_0 the erythrocyte count before treatment, expressed as millions of erythrocytes per cubic millimeter of blood

Adequate therapy is indicated by observed values which are equal to, or greater than, those obtained from this equation, observed values which are less than those calculated from this equation indicate inadequate treatment The occurrence of various complicating factors, such as concurrent disease, transfusion and hemorrhage, in association with pernicious anemia invalidates the use of this standard

In previous communications Schiødt³² has analyzed the regeneration of red blood cells in patients with hematemesis or melena from peptic

31 Riddle, M. C. Pernicious Anemia Erythrocyte Response to Treatment, *Am J M Sc* **200** 145, 1940

32 Schiødt, E. Observations on Blood Regeneration in Man V The Rise in Hemoglobin Compared with the Rise in Erythrocytes in Patients with Hematemesis or Melena from Peptic Ulcer, and in Patients with Pernicious and Hypochromic Anemia, *Acta med Scandinav* **104** 261, 1940

ulcer or with pernicious anemia In patients with pernicious anemia the starting point of measurement has been the day that treatment began In both forms of anemia, with uniform and adequate treatment, the daily rise is dependent on the lowest erythrocyte value in such a way that their relation may be expressed by the simple equation, "daily rise \times K = end value of regeneration — lowest value" The regeneration rate of hemoglobin may be expressed by a similar equation, and the regeneration of erythrocytes and of hemoglobin may thus be compared On the basis of this formula, curves showing regeneration of erythrocytes and hemoglobin in patients with hypochromic anemia, in those with hematemesis or melena from peptic ulcer and in those with pernicious anemia were constructed and compared The author concludes that when the initial level is taken into account, the increases in the red cell count and the hemoglobin percentage correspond fairly closely in cases of hemorrhagic and in cases of pernicious anemia In hypochromic anemia, which is secondary to chronic hemorrhage and to simple achylic anemia, however, regeneration of red cells follows the same lines as in other forms of anemia, but regeneration of hemoglobin lags far behind It was observed that in some cases of pernicious anemia the color index falls as the blood regenerates It is thought advisable to give iron in such cases

Alt and Young³³ are in agreement with the generally expressed belief that parenteral liver therapy is the treatment of choice for pernicious anemia, especially when degenerative changes in the spinal cord are present With adequate therapy, neural lesions are completely arrested and, in some cases, improvement in neurologic signs occurs Their own studies were concerned with observations on a group of 35 patients with pernicious anemia who had received parenteral liver extract therapy exclusively for a period varying from six months to eight years, the average duration being thirty-five months The following preparations were used 3 cc concentrated solution liver extract parenteral (Lederle), containing 10 U S P units, 1 cc concentrated solution liver extract parenteral (Lederle), containing 15 U S P units, solution liver extract, concentrated (Lilly), 3 cc containing 6 U S P units, and parenteral liver extract, 1 cc, with no U S P rating The authors conclude that pernicious anemia can be maintained in complete remission by injections of liver extract at intervals of two to three weeks Highly concentrated preparations are as effective as cruder ones in maintaining complete hematologic and neurologic remissions With adequate therapy neural lesions were arrested, and frequently improvement occurred For maintenance of the patient with pernicious anemia, a highly potent preparation should be used and the response of each person should

33 Alt, H L, and Young, R H Maintenance Treatment of Pernicious Anemia with Parenteral Liver Extract, *Illinois M J* 78 444, 1940

be studied. As a general rule it is advisable to give an excess of liver over the minimal requirement in order to provide a margin of safety against relapse.

Since liver therapy has been employed, it has been known that eosinophilia develops after the administration of raw liver but not after use of cooked liver. The increase in eosinophils usually varies between 20 and 40 per cent but has been known to reach as high as 74 per cent. When liver was given to patients who did not have pernicious anemia, similar eosinophilia occurred. That such a change may follow the oral use of liver extract is a controversial issue. There is no reference in the literature to its development following the parenteral use of liver extract. Allin and Meyer³⁴ found that of 279 patients with pernicious anemia treated at the State of Wisconsin General Hospital from 1925 to 1938, 224 received one or more forms of liver therapeutically. Patients with allergic states and parasitic infection had been excluded in each instance. Of this group of 224 patients, eosinophilia developed in 87 at some time or other. It is important to note, however, that eosinophilia of a lesser degree occurred in 24 of 45 patients in whom no allergy could be found and who had received no form of liver up to the time of discovery of the eosinophilia. Four control patients without systemic disease received a combination of liver extract and cooked liver. In only 1 did eosinophilia develop, this patient was given intramuscular injections of liver extract followed, after about seven weeks, by administration of cooked liver. Twenty-one days after intramuscular administration of liver extract had begun, the percentage of eosinophils was 7.75 per cent. Of the 5 previously untreated patients with pernicious anemia who received liver extract intramuscularly, eosinophilia developed in 1. Attempts to correlate a local dermal reaction with liver extract and the development of eosinophilia were unsuccessful. It was concluded that the allergic nature of the eosinophilia had not been demonstrated and that neither had this been excluded as a possibility. Further investigations are necessary to settle this question.

Strauss and Pohle³⁵ discontinued all antipernicious anemia therapy in a group of 15 patients with pernicious anemia who had been treated for about three years and whose red blood cell counts during this interval had remained continuously at 4,500,000 per cubic millimeter or higher. Previously, the patients had received 10 cc of liver extract intramuscularly every four weeks, prepared according to the method of Strauss, Taylor and Castle. Three of the patients showed no signs

34 Allin, R. N., and Meyer, O. O. Development of Eosinophilia Following Liver Therapy, *J. Lab. & Clin. Med.* **26**: 457, 1940.

35 Strauss, M. B., and Pohle, F. J. Duration of Remission in Pernicious Anemia with Liver Therapy. Efficacy of Massive Doses Administered at One Time, *J. A. M. A.* **114**: 1318 (April 6) 1940.

of anemia until nineteen, twenty-six and twenty-seven months, respectively, after liver therapy was stopped. In the remaining 12 patients anemia developed, with a red blood cell count of 4,000,000 or less per cubic millimeter, within a period of ten months. Three of these had a relapse in two months after liver therapy was omitted. At the time of the relapse each of the 12 patients received 160 cc of the same liver extract intramuscularly over a period of one week. This dose was 30 cc more than the amount which had been given in divided doses over the previous period of a year, during which time the red blood cell count had remained within normal limits. After this massive dose, each patient was seen at intervals of one month. Relapse occurred again in each patient in a period varying from two to twelve months. In general, the length of the remission appeared to be a function of the individual patient rather than of the treatment. The authors conclude that the majority of patients with pernicious anemia cannot be treated safely by injections of liver extract if the period between the treatments is too long, even if massive amounts are given. Treatments should be given at one to four week intervals, depending on the individual case. The authors emphasize the obvious difficulties involved in determining the potency of liver extracts by their maintenance effects.

Strauss, Solomon and Fox³⁶ studied the effect of intramuscular injections of liver extract on the neural manifestations of pernicious anemia. Their report is based on a study of 85 patients, observed for an average period of seven years. The patients received intramuscularly solution liver extract (Lilly) N N R prepared according to the method of Strauss, Taylor and Castle. It is estimated that this material contains about 1 injectable U S P unit per cubic centimeter. It is an aqueous solution of fraction G of Cohn and contains many substances present in liver other than the anti-pernicious-anemia principle. Most of the patients received 10 cc of this extract at weekly intervals, but others received as much as 10 cc three times weekly and some as little as 10 cc every three weeks. Twenty-one of the patients had severe involvement of the cord, as evidenced by spasticity or ataxia or both, resulting in definite disturbances of locomotion. Also, they had paresthesia of the hands and feet, diminution or absence of vibratory sensation in the legs and moderate to advanced muscular weakness. Impotence, which was thought to be attributable to pernicious anemia, was present in 5 patients. Girdle sensations were common. The treatment administered in this group of 21 patients with advanced changes in the cord was sufficient to prevent any objective neurologic signs from becoming more pronounced, nor did abnormal signs not previously

36 Strauss, M B, Solomon, P, and Fox, H J. Combined Degeneration of Spinal Cord in Pernicious Anemia. Results of Seven Years' Experience with Parenteral Liver Therapy, *New England J Med* 222 373, 1940

present appear in any of the patients with advanced involvement of the spinal cord. In other words, Strauss and his associates have demonstrated that adequate anti-pernicious-anemia therapy can completely arrest the neural manifestations of pernicious anemia. A second group who received this treatment consisted of 64 patients who did not have significant signs or symptoms of involvement of the nervous system. Over a period of seven years there was no evidence that further neural damage was done. These authors stress the fact that previous observers who stated that the neural involvement progressed despite adequate therapy did not use the proper criteria for adequate therapy. According to Strauss and his associates, treatment should be given so that the red blood cell count is maintained at a level of 4,500,000 per cubic millimeter, the mean corpuscular volume below 100 cubic microns and the color index at 1.0 or less. Furthermore, there should be no symptoms, such as glossitis or indigestion, attributable to pernicious anemia. If there should be a recurrence of the paresthesia of the extremities, the dose of the liver extract should be increased, usually doubled. If the patient presents any other symptoms which might possibly be due to changes in the spinal cord, the dose should be doubled. We are in complete accord with the concluding statement of the article.

By means of appropriate parenteral liver extract therapy for each case, the spinal-cord lesions of pernicious anemia may be prevented from developing, or, having appeared, may be completely arrested.

Pernokis³⁷ gives a routine description of the symptoms and signs of the disease and the usual laboratory findings. There are some statements with which we are not in accord, of which the one indicating that the spleen is palpable in 40 per cent of cases is an example. Data concerning this organ are presented in an article by Bigg, which is cited in this review. Furthermore, the treatment suggested is inadequate as the doses are too small, and we do not consider it necessary to give hydrochloric acid or iron medication to the average patient with the disease.

Evans³⁸ presents an excellent review of the clinical aspects of pernicious anemia and a résumé of the development of knowledge of the disease up to the introduction of the liver treatment by Minot and Murphy, in 1926.

MACROCYTIC ANEMIAS OTHER THAN PERNICIOUS ANEMIA AND THE OCCURRENCE OF THE LATTER IN THE TROPICS

Since 1932 a study of the tropical anemias as they occur in Puerto Rico has been in progress. Cases of macrocytic anemia have been

37 Pernokis, E. W. Pernicious Anemia, *Internat Clin* 2:216, 1940.

38 Evans, F. A. Clinical Aspects and Treatment of Pernicious Anemia, *Pennsylvania M J* 43:946, 1940.

observed which did not fit into the syndrome of sprue as it is most frequently seen in that region or into that of clinical pernicious, or addisonian, anemia of the temperate zones. The work of Wills on tropical anemia in India and that of Fairley and his co-workers on nutritional anemia in Macedonia suggested to Rodríguez-Molina³⁹ that these conditions probably fell into the category of disturbances which he designated as nutritional macrocytic anemia. He cites the unpublished observations of Hernandez Morales, in Puerto Rico, which show that in a study of the blood of 104 girls, 27 per cent were found to have macrocytic hyperchromic anemia and 28 per cent macrocytic hypochromic anemia. The anemia was mild and appeared to be correlated with a deficient diet. The case records of 2 colored women aged 60 and 48, respectively, suffering from tropical macrocytic anemia are reported. In both the anemia was severe, in 1 it was of the macrocytic hyperchromic type, whereas in the other it was of the macrocytic hypochromic variety. Although the blood pictures bore a close resemblance to those characteristic of sprue and pernicious anemia, it is thought by the author that this anemia could be distinguished from the latter two diseases. The condition is thought to be due to some deficiency of the diet, other than Castle's extrinsic factor. The parenteral use of crude liver extracts, which is effective in treatment of tropical anemia in India, is also efficacious for this type of anemia, as is autolyzed yeast extract given orally. When iron deficiency is present, iron sulfate is also recommended.

Azmy Pasha and Zanaty⁴⁰ are in agreement with the statement that pernicious anemia has a racial incidence, for it is generally regarded as a disease of the Nordic races and is less common among the southern races. According to them, it is rarely met with in Asiatics and is unknown in the tropics, its extreme rarity in Egypt has recently been emphasized. In the course of investigating many cases of anemia in Egypt, the authors encountered 1 which was thought to be an instance of true addisonian pernicious anemia. The patient was a man aged 34 who one year previously had suffered from a severe attack of diarrhea, with as many as twenty liquid stools daily. He recovered from this spontaneously and remained well for five months, then the onset of symptoms of severe anemia was followed by a recurrence of the diarrhea. The patient had a smooth, atrophic tongue and gave a history of recurrent glossitis. The spleen could be felt 1 fingerbreadth below the costal margin. Paresthesia of the limbs was the only neurologic manifestation. The red blood cell count was 1,000,000 per cubic millimeter, the hemoglobin concentration 32 per cent and the white blood cell count

39 Rodríguez-Molina, R. Tropical Macrocytic Anemia in Puerto Rico. Report of Two Cases, Puerto Rico J. Pub. Health & Trop. Med. **15** 177, 1939.

40 Azmy Pasha, S., and Zanaty, A. F. Pernicious Anaemia in Egypt, Lancet **2** 1359, 1939.

4,000 per cubic millimeter After an unsuccessful trial of iron therapy and the use of a liver preparation which contained autolyzed yeast extract (marmite) and iron, the patient was given 1 pound (453 Gm) of raw liver daily This medication caused a prompt reticulocyte response and an increase in the erythrocyte count and the hemoglobin percentage to normal A fractional test meal following the injection of histamine showed achlorhydria A bone marrow puncture, which gave the first clue to the diagnosis, showed megaloblastic hyperplasia, which changed to a normocytic picture with administration of liver extract The authors maintain that the patient did not have nutritional macrocytic anemia, as his diet was adequate and this syndrome has not been encountered in their experience in Egypt, even among the poorer classes

Manson-Bahr⁴¹ gives a complete review of the possible interrelationships of the clinical syndromes of pellagra, pernicious anemia, sprue, idiopathic steatorrhea and nutritional megalocytic anemia The reader is referred to his original papers for the interesting details presented According to the author, it has been shown that glossitis, probably of a similar nature and nonspecific to the disease, is found in each of the several diseases mentioned This pathologic change and additional clinical features which the diseases have in common, such as alterations in the nervous system, suggest that the syndromes are closely related On analogic and therapeutic grounds the author is inclined to regard the cause of the phenomena which are common to all as a deficiency of the vitamin G (B_2) complex He also suggests that nicotinic acid and riboflavin may play an important part in the treatment of this group of diseases He concludes that borderline conditions are often encountered which may embody the salient features of two or more of the group

MICROCYTIC ANEMIAS

Hypochromic Anemia and Iron Requirements—Experimental Studies A comprehensive review, chiefly of contributions to the literature during the past decade, dealing with metallic elements and their relation to blood formation has been published by Schultze⁴²

Austoni, Rabinovitch and Greenberg⁴³ describe a technic for vivipfusion of rats and give values for the iron content of various tissues Healthy and anemic rats receiving a standard diet under normal

41 Manson-Bahr, P H Glossitis and Vitamin B_2 Complex in Pellagra, Sprue and Allied States, *Lancet* **2** 317 and 356 1940

42 Schultze, M O Metallic Elements and Blood Formation, *Physiol Rev* **20** 37, 1940

43 Austoni, M E, Rabinovitch, A, and Greenberg, D M The Iron Content of the Tissues of Normal, Anemic, and Iron-Enriched Rats Freed from Blood by Vivipfusion, *J Biol Chem* **134** 17, 1940

conditions, as well as animals fed iron supplements and maintained under reduced oxygen tension, were utilized. The liver and the spleen exhibited the greatest depletion of the metal in anemic rats. The largest increase of iron occurred in the bone marrow of iron-enriched animals. Austoni and Greenberg⁴⁴ continued their studies with the aid of radioactive iron. Accumulation of the metal was demonstrated in the muscles of iron-fed anemic rats, and greater absorption of labeled iron was observed to occur in anemic than in normal animals. Twelve hours was required for the passage of a single dose of radioactive iron from the stomach through the small intestine. Passage through the alimentary tract was significantly slower in anemic rats, and the authors suggest that delayed passage may be a factor in the greater absorption by such animals. Less iron was excreted by anemic rats in both urine and feces. During a ten day period of observation normal animals retained about 30 per cent and anemic rats approximately 50 per cent of the radioactive iron administered. The greater part of the elimination occurred within forty-eight hours of administration. The specific accumulation per gram of tissue weight was greatest in the bone marrow, blood, spleen, liver and heart, whereas the largest total accumulation took place in the blood and muscle, particularly in the anemic animals. After ten days it was noted that radioactive iron was practically gone from the muscle and blood of normal rats, but 25 per cent of the administered dose remained in the muscle and 14 per cent in the blood of anemic animals.

Hahn and his associates⁴⁵ report confirmation of their previous observation that radioactive iron is detectable in circulating red blood cells of anemic dogs within four hours of its administration. They found that absorbed labeled iron was entirely converted into hemoglobin within four to seven days under standard anemic conditions. As the iron intake is increased the percentage of its absorption rapidly falls.

Interrelationships of iron, calcium and phosphorus metabolism have received consideration. Anderson, McDonough and Elvehjem⁴⁶ induced anemia in rats according to their usual procedure and placed the animals on basal diets with variable quantities of calcium, phosphorus, iron and copper. The results indicated that a low calcium-phosphorus ratio was favorable to utilization of iron. Maximum utilization occurred at a

44 Austoni, M. E., and Greenberg, D. M. Studies in Iron Metabolism with the Aid of Its Artificial Radioactive Isotope. The Absorption, Excretion and Distribution of Iron in the Rat on Normal and Iron-Deficient Diets, *J. Biol. Chem.* **134** 27, 1940.

45 Hahn, P. F., Ross, J. F., Bale, W. F., and Whipple, G. H. The Utilization of Iron and the Rapidity of Hemoglobin Formation in Anemia Due to Blood Loss, *J. Exper. Med.* **71** 731, 1940.

46 Anderson, H. D., McDonough, K. B., and Elvehjem, C. A. Relation of the Dietary Calcium-Phosphorus Ratio to Iron Assimilation, *J. Lab. & Clin. Med.* **25** 464, 1940.

ratio of 0.45, with continued decrease as a ratio of 7.65 was approached. Within ordinary limits of ingestion, and with most types of diet, calcium appears to impede the absorption of iron, whereas phosphorus exerts a favorable effect on its absorption. Barer and Fowler⁴⁷ observed no changes in the calcium, phosphorus and nitrogen balances of 16 patients with hypochromic anemia and 3 healthy persons during the administration of medicinal iron, either by mouth or by intramuscular injection.

Limited observations on mature dogs maintained on exclusive milk diets after induction of anemia by withdrawal of blood and on the iron requirements for hemoglobin formation of growing dogs led Frost and his collaborators⁴⁸ to the conclusion that copper supplements aid in the utilization of iron. Cobalt was found to exert a stimulative effect on hematopoiesis. From a study of the total iron content of rats Otis and Smith⁴⁹ concluded that a true sex difference existed in the utilization of iron. The variation cannot be explained on the basis of differences in the weights of the two sexes. During the curative period after induction of anemia by means of a milk diet more iron was stored by female than by male rats.

Lederer⁵⁰ found that the action of hydrochloric acid and a ferment was necessary for the release of the iron contained in egg yolk. In the gastric contents of patients with hypochromic anemia associated with achlorhydria the necessary ferment was lacking. Persons with pernicious anemia appeared to possess the ferment, but the iron of egg yolk was not released by the gastric secretion because of absence of hydrochloric acid.

The ability of dogs to produce new hemoglobin and plasma proteins was measured simultaneously by Robscheit-Robbins and her associates.⁵¹ The dogs were fed an excess of iron, and anemia was maintained by frequent bleeding. The protein content of the diet was low. It was found that when strong stimuli for the production of both new hemo-

47 Barer, A. P., and Fowler, W. M. The Effect of Iron on Phosphorus, Calcium, and Nitrogen Metabolism, *J. Lab. & Clin. Med.* **26** 351, 1940.

48 Frost, D. V., Potter, V. R., Elvehjem, C. A., and Hart, E. B. Iron and Copper Versus Liver in Treatment of Hemorrhagic Anemia in Dogs on Milk Diets, *J. Nutrition* **19** 207, 1940. Frost, D. V., Elvehjem, C. A., and Hart, E. B. Iron Utilization in Dogs on Milk Diets, *ibid.* **19** 311, 1940.

49 Otis, L., and Smith, M. C. Further Evidence of Sex Variation in the Utilization of Iron by Anemic Rats, *Science* **91** 146, 1940.

50 Lederer, J. Etude comparée de la libération du fer du jaune d'œuf par le suc gastrique de sujets normaux, de sujets atteints d'anémie hypochrome avec achylie et de sujets atteints d'anémie pernicieuse, *Compt. rend. Soc. de biol.* **132**. 491, 1939.

51 Robscheit-Robbins, F. S., Madden, S. C., Rowe, A. P., Turner, A. P., and Whipple, G. H. Hemoglobin and Plasma Proteins. Simultaneous Production During Continued Bleeding as Influenced by Diet Protein and Other Factors, *J. Exper. Med.* **72** 479, 1940.

globin and new plasma protein were present preference was given to manufacture of hemoglobin, no matter which of the food proteins tested by the authors was used

Earlier observations on hypochromic anemia induced by diets deficient in the crystalline factor I, apparently identical with the rat anti-dermatitis factor, vitamin B₆ (pyridoxine), have been extended by a number of workers Fouts, Helmer and Lepkovsky,⁵² who previously reported on this deficiency anemia in puppies, were able to produce the condition in adult dogs Hypochromic anemia resulting from lack of factor I failed to respond to administration of iron and copper Similar observations are reported by Borson and Mettier⁵³ These workers placed adult dogs on deficient diets supplemented by an excess of iron Hypochromic microcytic anemia developed and was corrected by a daily dose of 60 micrograms of vitamin B₆ (synthetic and natural) per kilogram of body weight, however, recovery was not complete when the diet was deficient in liver filtrate factors In such cases the addition of adsorbable factors, obtained from rice bran, failed to lead to improvement Hogan and associates,⁵⁴ on the basis of experimental observations, believe that lack of an unrecognized fraction of the vitamin B complex may be responsible for a specific anemia induced in pigeons

Application of vitamin B₆ therapy in cases of anemia in human beings has been carried out by Vilter, Schiro and Spies⁵⁵ The observations were limited, but the authors demonstrated that the intravenous administration of crystalline vitamin B₆ 50 to 100 micrograms in physiologic solution of sodium chloride to 3 pellagrins with macrocytic anemia and to 2 patients suffering with untreated pernicious anemia was followed by some increase in the number of circulating reticulocytes

Determinations of total iron on 2,608 samples of blood are reported by Walker and Fitz⁵⁶ Although the authors state that "a knowledge of the blood-iron level is proving in our experience of considerable practical interest," the impression gained from a survey of their published material indicates that the procedure, as employed, offers no

52 Fouts, P J , Helmer, O M , and Lepkovsky, S Nutritional Microcytic Hypochromic Anemia in Dogs Cured with Crystalline Factor I, *Am J M Sc* **199** 163 (Feb) 1940

53 Borson, H J , and Mettier, S R Relief of Hypochromic Anemia in Dogs with Synthetic Vitamin B₆ Influence of "Filtrate Factors," *Proc Soc Exper Biol & Med* **43** 429, 1940

54 Hogan, A G , Richardson, L R , Johnson, P E , and Nisbet, R N Pigeon Anemia as a Deficiency Disease, *J Nutrition* **20** 203, 1940

55 Vilter, R W , Schiro, H S , and Spies, T D Effect of Synthetic Vitamin B₆ on the Haemopoietic System of Human Beings, *Nature, London* **145** 388, 1940

56 Walker, B S , and Fitz, R Clinical Observations on Blood Iron, *Ann Int Med* **14** 263, 1940

more than a rather cumbersome approach to an expression of the hemoglobin value

Hypochromic Anemia in Adults The relationship of iron metabolism to anemia and its therapy is discussed by Fowler and Barer⁵⁷ They present a résumé of their previously published experimental work and conclude that the dietary iron should approximate 12 to 15 mg per day in order to insure adequate absorption The three primary factors which, according to the authors, determine the need for iron are its loss by hemorrhage, its loss by excretion and formation of new iron-containing tissue They found that the larger the dose of medicinal iron administered, the smaller was the percentage of the metal absorbed, but, within limits of toleration, the greater was the total quantity retained and utilized in formation of hemoglobin

Further observations on blood regeneration have been published by Schjødt⁵² He found that the rates of increase of erythrocytes and hemoglobin observed in cases of pernicious anemia and of acute hemorrhagic anemia were comparable The rise in red cells in cases of chronic hemorrhagic anemia and simple achylic anemia agreed closely with that noted in cases of the aforementioned types, but the increase in hemoglobin in cases of the latter anemias lagged far behind

A high incidence of anemia among Chinese professional blood donors is reported by Snapper and his co-workers⁵⁸ Leukopenia, lymphocytosis and eosinophilia were frequently observed Inadequate nutrition, in conjunction with loss of blood, was considered a factor in the causation of the anemia Responses were obtained to iron medication

The syndrome of dysphagia and chronic hypochromic microcytic anemia, usually associated with achlorhydria (the Plummer-Vinson syndrome), has attracted recent attention among laryngologists Gerlings⁵⁹ describes 6 cases of this disorder, in all of which roentgenologic examinations and in 5 of which esophagoscopic studies were made Stenosis of the esophagus, superficial ulcerations and cicatrices were observed In some instances stagnation of secretion occurred above the entrance to the esophagus The author points out the possibility of precancerous lesions in this condition Corday⁶⁰ observed hyper-

57 Fowler, W M, and Barer, A P Iron Metabolism and Its Relationship to Anemia and Therapy, *Ann Int Med* **14** 378, 1940

58 Snapper, I, Lin, S H, Chung, H L, and Yu, T F Anemia from Blood Donation Hematological and Clinical Study of One Hundred and One Professional Donors, *Chinese M J* **56** 403, 1939

59 Gerlings, P G Disorders of the Mouth of the Esophagus in the Syndrome of Plummer-Vinson (Dysphagia with Anaemia), *J Laryng & Otol* **55** 143, 1940

60 Corday, D P The Plummer-Vinson Syndrome, *Ann Otol, Rhin & Laryng* **49** 160, 1940

keratinization of the epithelium of the esophagus of rats, associated with a moderate degree of anemia, after the animals had been maintained on an exclusive milk diet for five and one-half months. No web formation was found. The author suggests that in human subjects the primary lesion is an esophageal web which interferes with nutrition and thereby leads to anemia. The prolonged low blood values, he thinks, are responsible for secondary esophageal changes, which may be precancerous. Two cases are reported by Kernan⁶¹ as instances of the Plummer-Vinson syndrome, but the data submitted fail to substantiate this diagnosis.

The association of anemia and diaphragmatic hernia of the stomach continues to excite interest because the pathogenesis of the hemoglobin deficiency, although often related to loss of blood, is not always clear. Schiro and Benjamin⁶² report a case in which gastroscopic findings included decreased prominence of rugae, some of which were abnormally red. Erosions and ulcerations were not observed, and no difference was seen in the mucosa above and that below the diaphragm. Occult blood was, however, present in the feces. Two sisters of this patient also suffered with diaphragmatic hernia. Dyke and Dyas⁶³ report 2 cases of diaphragmatic hernia of the stomach with hypochromic anemia. The lowered blood values are attributed by the authors to changes in the gastric mucosa rather than to hemorrhage, although occult blood was found in the stools. The anemia responded to iron therapy. The case of a patient with this condition complicated by angina pectoris is described by Ernstene and McGurl⁶⁴. With correction of the anemia by means of iron therapy the angina disappeared.

Murphy and Damarjian⁶⁵ report a case of severe hypochromic anemia in which there was clinical evidence, supported by response to specific treatment, of both iron and riboflavin deficiency.

The almost universal incidence of anemia among the coolie population of the tea estates of Assam is discussed by Hare⁶⁶. The anemia is usually microcytic and is attributed to prolonged dietary deficiency.

61 Kernan, J. D. Plummer-Vinson Syndrome. Report of Two Cases, *Arch Otolaryng* **32** 662 (Oct) 1940.

62 Schiro, H. S., and Benjamin, J. E. Severe Anemia Associated with Diaphragmatic Hernia, *Ohio State M. J.* **36** 164, 1940.

63 Dyke, S. C., and Dyas, G. E. Herniation of the Stomach with Anaemia, *Lancet* **1** 119, 1940.

64 Ernstene, A. C., and McGurl, F. J. Esophageal Hiatus Hernia Associated with Hypochromic Anemia and Angina Pectoris. Report of Case, *Cleveland Clin. Quart.* **7** 209, 1940.

65 Murphy, R. G., and Damarjian, E. Riboflavin Deficiency with Idiopathic Hypochromic Anemia, *Rhode Island M. J.* **23** 114, 1940.

66 Hare, K. P. Clinical Investigations into Anaemia in Assam, *Indian J. M. Research* **27** 1041, 1940.

Hookworm infection and malaria, although prevalent, cannot be incriminated as the sole etiologic factors. In the less common macrocytic anemias, which occur most often during pregnancy, the responsible factor is thought to be a combination of nutritional inadequacy, the presence of the fetus and the effect of chronic malaria operating on an already inefficient hemopoietic system.

The subject of anemia following gastrectomy has been reviewed by Jones.⁹ Other articles of a general nature dealing with the treatment of hypochromic anemia have been published by Eckman,⁶⁷ Heck,⁶⁸ Creskoff,⁶⁹ Grove,⁷⁰ Hume⁷¹ and others.⁷²

Hypochromic Anemia in Children Observations continued over several years on the incidence, etiologic factors and treatment of anemia associated with hookworm infection in school children are reported by Payne and Payne.⁷³ The administration of medicinal iron, without elimination of the parasites, was followed by rapid and striking increases in the hemoglobin value. However, if the worms were not removed a definite fall in the hemoglobin level occurred within five months after the discontinuance of iron therapy. After anthelmintic treatment alone a slow rise of hemoglobin occurred and a satisfactory level was reached in one to two years. Anthelmintic treatment supplemented by iron therapy produced the best results.

A survey of the blood status of children residing in Manchester, England, is reported by Somerford.⁷⁴ She found an incidence of anemia of 58 per cent among 201 subjects ranging in age from 10 weeks to 14 years. Lowered blood values were slightly more prevalent among boys than among girls, and the anemia was usually normocytic and normochromic. The leukocyte counts of the patients were normal. Sixteen

67 Eckman, P. F. Indications for Use of Iron in Treatment of the Anemias, *Minnesota Med* **23** 712, 1940.

68 Heck, F. G. Iron Requirements in Childhood and Adult Life, *Texas State J Med* **36** 286, 1940.

69 Creskoff, A. J. The Treatment of Anemias Other than Addisonian Pernicious Anemia, *Pennsylvania M J* **43** 1697, 1940.

70 Grove, W. E. Otolaryngologic Aspects of Blood Dyscrasias, *Wisconsin M J* **39** 188, 1940.

71 Hume, W. E. The Modern Treatment of Anaemia, *Practitioner* **145** 373, 1940.

72 Conferences on Therapy (From Cornell University Medical College and New York Hospital). Treatment of Blood Disorders, Microcytic Anemia, *J A M A* **114** 2544 (June 29) 1940.

73 Payne, G. C., and Payne, F. K. Relative Effectiveness of Iron and Anthelmintics in the Treatment of Hookworm Anemia, *Am J Hyg (Sect D)* **32** 125, 1940.

74 Somerford, A. E. Nutritional Anaemia. A Further Survey of Debilitated Children in Manchester, *Brit J Child Dis* **37** 1, 1940.

children suffered with microcytic and hypochromic anemia. No correlation was established between hemoglobin deficiency of the children and that observed in their mothers. Economic status and size of the family bore no evident relation to the incidence of anemia. Frequently 1 child in a family was anemic, whereas others exhibited normal blood values. Nutritional deficiency and anemia were not clearly correlated.

Crowley and Taylor⁷⁵ observed in 12 children between 6 and 12½ years of age iron-resistant hypochromic or normochromic anemia associated with a low inorganic phosphorus content of the blood, without clinical evidence of rickets. Administration of vitamin D restored the blood phosphorus value to normal in one month but had no effect on the hemoglobin level. When, however, the vitamin was given in conjunction with ferrous sulfate the hemoglobin was raised from an average of 79 per cent to one of 89 per cent (Haldane) in one month.

Congenital diaphragmatic hernia is an occasional cause of severe anemia in early childhood, and unless the possibility of this condition is borne in mind the diagnosis may easily be overlooked. The subject is discussed by Ladd and Gross,⁷⁶ and interesting cases are reported by Wolff⁷⁷ and by Grenet and his associates.⁷⁸

Over a period of ten years 6 cases of severe hypochromic anemia were observed in young girls by Alsted.⁷⁹ No evident cause for the anemia was found, and the author ascribes its development to qualitative and quantitative deficiencies of the diet. Excellent responses were obtained to large doses of iron. The clinical and hematologic features presented by these patients fit the description of chlorosis, but the author prefers the designation of essential hypochromic anemia.

Two cases of severe anemia, occurring in a brother and sister, each at the age of 8, are reported by Hjorth.⁸⁰ The findings included hyperchromic anemia, leukopenia, thrombopenia, hemorrhagic diathesis, congenital bone deformities and hypoplasia of the bone marrow, thymus and testes. Life was maintained only by frequently repeated blood transfusions. A high incidence of congenital bone deformities was discovered in the members of the mother's family. The interesting mesoblastic anomaly arachnodactyly (Marfan's syndrome), with severe anemia, was

75 Crowley, N, and Taylor, S. Iron-Resistant Anaemia and Latent Rickets in School Children, *Arch Dis Childhood* **14** 317, 1939.

76 Ladd, W. E., and Gross, R. E. Congenital Diaphragmatic Hernia, *New England J. Med.* **223** 917, 1940.

77 Wolff, S. Diagnostic Errors, *Brit J Child Dis* **37** 16, 1940.

78 Grenet, H., Isaac-Georges, P., and Combes-Hamelle. Hernie diaphragmatique droite a forme anémique, *Bull Soc de pédiat de Paris* **37** 420, 1939.

79 Alsted, G. Essential Juvenile Hypochromic Anemia (Chlorosis), *Nord med (Hospitaltid)* **7** 1338, 1940.

80 Hjorth, P. Two Cases of Constitutional Anemia in Children, *Nord med (Hospitaltid)* **7** 1313, 1940.

observed in a 16 year old girl by Olcott⁸¹ At autopsy the spleen was found to be small, but the bone marrow was described as moderately hyperplastic The mechanism responsible for the severe hypochromic and non-resistant anemia was obscure

The anemias of infancy and childhood are discussed by Rittershofer,⁸² who states that nutritional anemia is most common between the ages of 6 months and 2½ years The condition, he recommends, should be treated with simple iron preparations, and he finds that the supplementary use of copper is generally unnecessary An authoritative general article on the subject, with a useful review of the recent literature, has been published by Smith⁸³

ANEMIA IN PREGNANCY

Labate⁸⁴ studied the blood values for 19 women from the thirty-eighth week of gestation to the tenth day after confinement After delivery increases in the erythrocyte count, hemoglobin concentration, hematocrit reading and plasma protein values were observed It was found that when the erythrocyte count and the hematocrit values were restored to normal nonpregnant limits the value for hemoglobin averaged 9 per cent less than the lower limit of normal

A review of the present status of information regarding anemia of pregnancy in India was published by Napier⁸⁵ The author states that the high mortality of Indian women in childbirth is due in part to anemia It occurs with greater frequency and severity during the second half of the year and is most pronounced in the third trimester of gestation The incidence is slightly greater in primiparas than in multiparas Anemia is almost always associated with edema, fever occurs in one-half the women, and albuminuria is found in 25 to 50 per cent of them There is a relatively high incidence of splenomegaly Three common types of anemia are described (1) microcytic hypochromic form, attributed to diet defects or loss of blood associated with hookworm infection, (2) macrocytic hyperchromic form, believed to result from the dietary lack of substances present in autolyzed yeast and crude liver extract, not associated with achlorhydria, the indirect van den Bergh

81 Olcott, C T Arachnodactyly (Marfan's Syndrome) with Severe Anemia, *Am J Dis Child* **60** 660 (Sept) 1940

82 Rittershofer, C R The Anemias of Infancy and Childhood, *Ohio State M J* **36** 1309, 1940

83 Smith, C H Management of the Anemias in Infancy and Childhood, *Bull New York Acad Med* **16** 525, 1940

84 Labate, J S Blood Studies During Pregnancy and Puerperium, *Am J. Obst & Gynec* **39** 87, 1940

85 Napier, L E, Anemia in Pregnancy in India The Present Position, *Indian J M Research* **27** 1009, 1940

reaction of neurologic lesions and not amenable to treatment with purified liver extract, and (3) another type of macrocytic hyperchromic anemia, with evidences of hemolysis, probably associated with chronic malaria and some nutritional deficiency

An account of anemia of pregnancy in India is also given by Chatterjee⁸⁶ He has observed that it is most prevalent during the rainy season, in the summer Four stages in the development of the anemia are described (1) normocytic, the mildest manifestation observed, (2) microcytic, (3) microcytic or normocytic but hyperchromic, and (4) macrocytic and hyperchromic This last stage the author associates with failure of the bone marrow The administration of iron is of value in stages 1 and 2, and liver extract is efficacious in stage 3, but it has been the usual experience that blood transfusions offer the only hope of improvement to patients suffering with anemia in stage 4 The author found the serum albumin low and the globulin (euglobin fraction) high in cases of macrocytic hyperchromic anemia Normally, during pregnancy the blood cholesterol level is elevated, but in patients with this form of anemia lowered values were obtained The author treated 14 patients with intramuscular injections of 2 cc of a 5 per cent solution of cholesterol in olive oil every other day During a course of therapy lasting about two months the average erythrocyte level rose from 850,000 to 3,500,000 per cubic millimeter Patients serving as controls received liver extract by intramuscular injection and iron preparations by mouth, without response

A review of recent contributions to the subject of anemia in pregnancy has been published by Sodeman⁸⁷

HEMOLYTIC ANEMIA

No etiologic classification of hemolytic anemia is wholly satisfactory, since in many cases the cause is either obvious or entirely obscure The clinical differentiation of such anemias as congenital and acquired, with further separation into acute and chronic forms, is serviceable, although it should be borne in mind that the same provocative agent or hemolytic mechanism may underlie varied clinical manifestations Dameshek and Schwartz⁸⁸ have reviewed the literature dealing with acute hemolytic anemia, in conjunction with a report of 4 cases which they studied extensively They call attention to the earlier work of French investigators, particularly Chauffard, Widal and Troisier, whose studies

86 Chatterjee, H N Anemia of Pregnancy in India Its Treatment with Cholesterol, *Lancet* **1** 14, 1940

87 Sodeman, W A Anemia in Pregnancy, *Am J M Sc* **200** 117, 1940

88 Dameshek, W, and Schwartz, S O Acute Hemolytic Anemia (Acquired Hemolytic Icterus, Acute Type), *Medicine* **19** 231, 1940

of acute acquired hemolytic states were largely ignored by subsequent authors. Dameshek and Schwartz conclude that the association of spherocytosis, increased fragility, reticulocytosis and response to splenectomy is not pathognomonic of congenital hemolytic anemia but may occur in the acquired type and may be reproduced experimentally. Spherocytosis and increased fragility they attribute to the effects on the normal, mature red blood cells of a lytic agent. In support of this view they were able to demonstrate isohemolysins in the serum in 2 of their 4 cases. Such hemolysins were effective against cells of group O and against cells of the same group in which the hemolysins occurred. They state that splenectomy is almost universally of value in the treatment of acute acquired hemolytic anemia due to the presence of hemolysins. The operation was reported as curative in 20 of 23 cases collected from the literature. Pathologic examination of the spleens in these cases revealed three types of change: (1) multiple areas of thrombosis and infarction, (2) histiocytic proliferation, often with erythrophagocytosis and giant cell formation, and (3) congestion of the pulp. Extreme normoblastic hyperplasia of the bone marrow was a general finding.

The nonspecificity of spherocytosis and decreased erythrocyte resistance to hypotonic solutions of sodium chloride in chronic hemolytic anemia of the congenital or familial type are also emphasized by Tigertt and Hill⁸⁹. They state, furthermore, that these abnormalities are not requisite to the diagnosis of such anemia. Tigertt, Duncan and Hight⁹⁰ were able to produce microspherocytosis and increased erythrocyte fragility in dogs by the injection of specific hemolysins. Bimodal frequency distribution curves for erythrocyte diameter were obtained. Such curves are explained by the simultaneous occurrence of small spherocytes and large reticulocytes and have been observed also by Dameshek.

Whatever the role of splenectomy may be in effecting cessation of abnormal destruction of red cells, whether one of simple removal of erythroclastic cells or one of elimination of the site of hemolysin formation, evidence accumulates that the value of the operation is not limited to cases in which microspherocytosis and increased fragility are exhibited. Such a case is reported by Fairar, Burnett and Steigman⁹¹. In that

89 Tigertt, W. D., and Hill, J. M. New Concepts of the Etiology of Hemolytic Anemia and Their Relation to Diagnosis, *Texas State J Med* **36** 214, 1940.

90 Tigertt, W. D., Duncan, C. N., and Hight, A. J. Erythrocyte Morphology in Experimental Hemolytic Anemia as Induced by Specific Hemolysin, *Am J M Sc* **200** 173, 1940.

91 Fairar, G. E., Jr., Burnett, W. E., and Steigman, A. J. Hemolytic Anemia and Hepatic Degeneration Cured by Splenectomy, *Am J M Sc* **200** 164, 1940.

instance a specific hemolysin was demonstrated Hurley and Moore⁹² cured by splenectomy a 33 year old man who had suffered from intermittent jaundice and anemia all his life, although the erythrocytes were normal in shape and in their response to hypotonic solutions of sodium chloride

The cases of a series of patients with the classic characteristics of congenital hemolytic jaundice are reported by Sharpe⁹³ Of 28 patients, 11 were males and 17 females, their ages ranged from 3 to 63 years, and the onset of symptoms was usually before the age of 20 Thirteen patients underwent splenectomy, and in each case the operation was followed by recovery from anemia and jaundice Seventeen cases of chronic hemolytic jaundice are discussed by Navarro and Cruz⁹⁴ In two thirds of them increased erythrocyte fragility was demonstrated

A résumé of his earlier observations and conclusions relating to hemolytic anemia is given by Haden⁹⁵ He also describes the cases of a mother and 2 children suffering with icterus, reticulocytosis and hemoglobinemia The red cells of these patients exhibited no spherocytosis and no decreased resistance to hypotonic solutions of sodium chloride, but they were said to hemolyze more readily than normal cells under other, unstated laboratory conditions The mother's mother was said to have died in early life of jaundice, anemia and splenomegaly Haden also discusses the Marchiafava-Micheli type of hemolytic anemia This disorder and that manifested in the cases reported he ascribes to a qualitative defect, other than abnormality of shape, inherent in the erythrocyte Haden states that hemoglobinemia and hemoglobinuria are evidence of intravascular hemolysis and that their presence contraindicates splenectomy However, in the opinion of Dameshek and Schwartz, free hemoglobin in the plasma and urine may result from higher concentration of the same hemolysin which in other cases may give rise to urobilinuria, bilirubinemia, spherocytosis and increased fragility Since evidence indicates that in many cases the spleen is concerned with the production of such hemolysins, intravascular hemolysis should not constitute the sole grounds for foregoing splenectomy

The appearance of rouleaux in fresh unmodified blood may be of diagnostic aid in cases of hemolytic anemia, according to Dameshek⁹⁶

92 Hurley, A G, and Moore, W C Congenital Hemolytic Jaundice Report of a Case with Normal Fragility and Normal Reticulocyte Count, Cured by Splenectomy, *Ann Surg* **112** 392, 1940

93 Sharpe, J C Hemolytic Jaundice A Clinical Analysis of Twenty-Eight Cases, *Ann Int Med* **14** 953, 1940

94 Navarro, R J, and Cruz, J R Hematologic Findings in Chronic Hemolytic Anemia (Familial Jaundice), *J Philippine M A* **20** 566, 1940

95 Haden, R L Hemolytic Anemia, *J Lab & Clin Med* **26** 65, 1940

96 Dameshek, W Rouleaux Formation in Fresh, Unmodified Blood as a Diagnostic Test for Hemolytic Anemia, *New England J Med* **221** 1009, 1939

Spherocytosis is associated with short, bizarre rouleaux and the increased thickness of some of the cells is apparent.

Increased endogenous metabolism of uric acid, a consequence of accelerated destruction of red cells, has suggested to numerous observers that the occasional association of gout and hemolytic jaundice is more than coincidental. Between 1934 and 1939, according to Deitrick⁹⁷ there were observed in the New York Hospital 22 patients suffering from gout without jaundice and 24 patients with congenital hemolytic jaundice. Three patients suffering from both diseases were encountered. Of these 3, 2 had nephritis and died in uremia and 1 underwent splenectomy and obtained complete relief from both hemolytic anemia and gout during a subsequent seven year period of observation. Lambie⁹⁸ reports the case, with unusually complete and detailed studies, of a man of 20 who had suffered with anemia from birth and had his first attack of gout at the age of 14. The anemia was of hemolytic type, but spherocytosis and increased fragility were not found. Splenectomy was followed by remission, with subsequent exacerbation, of the anemia. The author reviews the literature, including reported instances of gout in association with other blood disorders, particularly leukemia and erythremia.

The hemolytic action of sulfanilamide and its derivatives is well recognized. Why red cell destruction occurs much more readily and proceeds to far greater lengths in some patients than in others is not understood. A Negro, observed by Spence and Roberts,⁹⁹ received 28 Gm of sulfanilamide over a five day period in the treatment of a gonorrheal perineal abscess. The red cell count declined to 1,240,000 per cubic millimeter and the hemoglobin concentration to 21 per cent, 52 per cent of the erythrocytes were reticulated. The leukocytes numbered 140,000 per cubic millimeter, and myeloblasts and myelocytes were observed. The patient recovered. Ravid and Chesnei¹⁰⁰ report the case of a 79 year old man, suffering from pneumonia, who was given a total of 8 Gm of sulfapyridine (2-[paraaminobenzenesulfonamido] pyridine)

97 Deitrick, J. E. The Association of Congenital Hemolytic Icterus and Gout, *Internat Clin* **3** 264, 1940.

98 Lambie, C. G. A Study of Juvenile Gout in a Patient Suffering from Chronic Erythronoclastic Anemia of Obscure Origin, Together with Observations upon the Physical State of Uric Acid in the Blood and the Effects of Splenectomy, *M J Australia* **1** 535, 1940.

99 Spence, H. M., and Roberts, G. M. Extreme Leukocytosis and Acute Hemolytic Anemia Associated with the Administration of Sulfanilamide. Report of a Case, *New England J Med* **222** 874, 1940.

100 Ravid, J. M., and Chesnei, C. A Fatal Case of Hemolytic Anemia and Nephrotic Uremia Following Sulfapyridine Administration, *Am J M Sc* **199**, 380, 1940.

in two days. The sequence of events which followed included jaundice, anemia, hematuria, hemoglobinuria, anuria and uremia. The patient died sixty-five hours after administration of sulfapyridine. Necropsy revealed blocking of the renal tubules with hemoglobin derivatives, a condition frequently observed after transfusions of incompatible blood. A similar fatality following the administration of 25 Gm of sulfanilamide in the treatment of erysipelas was reported by Tragerman and Goto.¹⁰¹

Hemolytic anemia has been induced in rats by the administration of sulfanilamide, as reported by Higgins and Machella,¹⁰² and in rabbits by ingestion of indole, as reported by Taylor.¹⁰³

SICKLE CELL ANEMIA

Conditions affecting the sickling phenomenon in vivo and in vitro have been studied by Sherman.¹⁰⁴ He observed acceleration of sickling in the presence of increased leukocyte concentration, elevation of temperature and bacterial contamination, whereas the change was retarded by dilution of blood with an isotonic solution of sodium chloride and by increased oxygen tension. Sick cells were found regularly in high percentage in the venous circulation of patients with sickle cell anemia, but not of those with the sickling trait in the absence of anemia. When anemia was present the percentage of sickle cells was always greater in the venous than in the arterial circulation. It was found that the following solutions were equally efficacious as fixatives of the sickle cell: a 10 per cent concentration of solution of formaldehyde U S P in physiologic solution of sodium chloride, Zenker's stock solution, and Zenker's stock solution prepared with glacial acetic acid and with solution of formaldehyde U S P. Sherman describes a granular, or "holly wreath," type of cell occurring in the blood of persons with sickle cell anemia or the sickling trait. He differentiates the anemia from the trait by the following criteria: 1. The trait becomes evident only at much lower oxygen tension than does the anemia. 2. In the anemia, but not in the presence of the trait, sickle cells are found in the venous circulation and in blood placed in solution of formaldehyde U S P (1:10) under oil.

¹⁰¹ Tragerman, L. J., and Goto, J. M. Fatal Reactions to Administration of Sulfonamide Drugs. Report of Five Cases, *J. Lab. & Clin. Med.* **25** 1163, 1940.

¹⁰² Higgins, G. M., and Machella, T. E. The Bone Marrow of Rats Made Anemic by Administration of Sulfanilamide, *Anat. Rec.* **75** 529, 1939.

¹⁰³ Taylor, W. T. Blood Changes Produced in Rabbits by Indol, *M. Ann. District of Columbia* **8** 362, 1939.

¹⁰⁴ Sherman, I. J. The Sickling Phenomenon, with Special Reference to the Differentiation of Sickle Cell Anemia from the Sickle Cell Trait, *Bull. Johns Hopkins Hosp.* **67** 309, 1940.

Detection of the sickle cell trait has received the attention of Diggs and Pettit¹⁰⁵ For general purposes they recommend the method of Scriver and Waugh, in which after stasis is induced in a finger a drop of blood is removed and examined in a moist sealed preparation

The occurrence of sickle cell anemia in an Italian family of Sicilian origin is reported by Greenwald and Burrett¹⁰⁶ Twenty-three members of the family were examined, of these, 5 were found whose erythrocytes underwent sickling and 2 suffered with actual anemia

Skoog¹⁰⁷ reports the case of a 34 year old Negro with sickle cell anemia in whom complete hemiplegia developed, with persistent motor aphasia and palsy of several cranial nerves The blood and spinal fluid gave negative results when tested for evidence of syphilis The author attributes the multiple cerebral lesions to the occurrence of thromboses induced by the sickle cell abnormality The subject of involvement of the nervous system in sickle cell anemia is reviewed by Hughes, Diggs and Gillespie¹⁰⁸ They discuss in detail 25 cases previously reported in the literature and add 6 new cases, in 2 of which necropsy was done They conclude that involvement of the central nervous system is a frequent complication of sickle cell anemia and that the prognosis is poor, although the course is unpredictable The location of the lesions and the clinical manifestations are variable, the onset is often sudden and may be characterized by convulsions, meningeal signs, pain, aphasia, paralyzes, coma and death It is the authors' opinion that the lesions are primarily intravascular and due to thrombosis, which has followed extensions of the thrombotic process and hemorrhagic, degenerative and atrophic changes

Cummer and LaRocco¹⁰⁹ point out that sickle cell anemia should be considered as a possible explanation for chronic ulcers on the legs, especially in young persons Ulcers in patients with sickle cell anemia, they state, are limited almost entirely to those who have actual anemia

ERYTHROBLASTIC AND RELATED ANEMIAS

Three cases, each illustrative of a form of erythroblastic anemia, are reported by Wang and Khoo¹¹⁰ All occurred in Chinese infants and

105 Diggs, L W, and Pettit, V D A Comparison of Methods Used in the Detection of the Sickle Cell Trait, *J Lab & Clin Med* **25** 1106, 1940

106 Greenwald, L, and Burrett, J B Sickle-Cell Anemia in a White Family, *Am J M Sc* **199** 768, 1940

107 Skoog, A L Cerebral Complications in Sickle Cell Anemia, *South M J* **33** 714, 1940

108 Hughes, J G, Diggs, L W, and Gillespie, C E The Involvement of the Nervous System in Sickle Cell Anemia, *J Pediat* **17** 166, 1940

109 Cummer, C L, and LaRocco, C J Ulcers of the Legs in Sickle Cell Anemia, *Arch Dermat & Syph* **42** 1015 (Dec) 1940

110 Wang, C, and Khoo, F Hemolytic Anemia with Erythroblastemia A Report of Three Cases Seen in Chinese Infants, *Chinese M J* **58** 177, 1940

were characterized by anemia with erythroblastemia, reticulocytosis, leukocytosis, active erythropoietic hyperplasia of the bone marrow, increased fecal urobilin, splenomegaly and hyperplastic changes in the skull. One patient suffered with nutritional deficiency and chronic infection and recovered after appropriate therapy (von Jaksch's type). The outcome in the other 2 cases was fatal, although blood transfusions were of transient benefit, in 1 of them the features of erythroblastosis foetalis were exhibited, whereas in the other the condition was suggestive rather of Cooley's anemia.

Severe anemia, reticulocytosis, bilirubinemia, urobilinemia and splenomegaly characterized the 3 cases described by Abt¹¹¹. In 1 case the patient was 4 months old, and in the other 2 the children were each 1 year of age. Increased erythrocyte fragility and spherocytosis were not observed. The author states that the disorder may be familial but is not hereditary and that the mechanism of hemolysis is unknown. He considers transfusions of value as temporary aids and removal of the spleen as usually curative. Two of Abt's patients underwent splenectomy, with subsequent recovery.

Wayman¹¹² observed 2 infants, a sister and a brother, born a year apart, both suffering with icterus gravis and erythroblastemia. The first born died, whereas the second recovered after treatment with vitamin K, given because of evidence of obstructive, as well as hemolytic, jaundice and hemorrhagic manifestations.

During the past year there have appeared an unusual number of general discussions and reviews dealing in part with the erythroblastic anemias of infancy¹¹³. Of these the article by Smith^{113h} is outstanding for its scholarly and informed treatment of a complex subject.

In 1938 Barrett¹¹⁴ described an erythrocyte variant characterized by unusual thinness, increased resistance to hypotonic solutions of sodium

111 Abt, A. F. Hemolytic Disease in Infants, *Am J Dis Child* **60** 812 (Oct) 1940.

112 Wayman, E. W. Erythroblastosis in Icterus Gravis Neonatorum Successfully Treated with Vitamin K, *J Pediat* **17** 806, 1940.

113 (a) Tyson, R. M. Blood Dyscrasias of Infancy and Childhood, *Mississippi Doctor* **17** 589, 1940. (b) Atkinson, F. R. B. Lederer's Anaemia, *Brit J Child Dis* **37** 35, 1940. (c) Dwyer, H. L., and Neff, F. C. Anemia of the Newborn, *South M J* **33** 246, 1940. (d) Ruiz, C. Anemia idiopatica del recién nacido, *Arch argent de pediat* **11** 65, 1940. (e) Wellmeier, H. Blood Dyscrasias of Infancy and Childhood, *Ohio State M J* **36** 1078, 1940. (f) Reading, B. Anemias of the New Born Period, *Texas State J Med* **36** 405, 1940. (g) Anemias of the Newborn (Symposium), *Internat M Digest* **36** 247, 1940. (h) Smith, C. H. The Anemias of Early Infancy, *J Pediat* **16** 375, 1940.

114 Barrett, A. M. Special Form of Erythrocyte Possessing Increased Resistance to Hypotonic Saline, *J Path & Bact* **46** 603, 1938.

chloride and a target-like appearance in dried blood films, due to concentric dark and light zones. The occurrence of this cell is not limited to a single clinical disorder, but it is possible that those conditions in which it is found are due to related abnormalities of erythrocyte structure. Interesting publications dealing with this subject have recently appeared. Wintrobe and his associates¹¹⁵ report the observation in 14 persons, members of 3 Italian families, of a chronic disturbance of erythropoiesis characterized by microcytosis and hypochromia, bizarre red cell forms and increased resistance to hypotonic solutions of sodium chloride. In 8 subjects target cells were found. Three generations in one family and two in another were affected. The authors discuss the probable relationship of this condition to Cooley's anemia, sickle cell anemia and congenital hemolytic jaundice. As in Cooley's anemia, there appears to be an inherited defect in the production of erythrocytes whereby corpuscles are formed with an adequate or excessive membrane enclosing little substance. Other changes in the blood are attributed to attempts at compensation for the faulty red cell formation. In a footnote to their article they report observing a child with typical Cooley's anemia. Both of the child's parents were found to have target cell anemia.

Dameshek¹¹⁶ reports the case of an Italian youth aged 20 who was known to have suffered with hemolytic anemia and splenomegaly since the age of 5. Generalized osteoporotic changes were found, with thickening of the skull and a bony rib tumor. Many of the red cells were of the target type, extremely thin, with a tendency to buckle and ability to withstand hemolysis at exceedingly low concentrations of sodium chloride. Nucleated erythrocytes were not seen. The author believes that target cell anemia may be a late and relatively mild form of Cooley's anemia. He considers that these conditions, together with sickle cell anemia, form a group in which target cells and increased resistance to hypotonic solution of sodium chloride are the common denominators. None of these types of hemolytic anemia is benefited by splenectomy.

A detailed case report of a patient exhibiting severe hemolytic anemia, with 47.5 per cent of the red cells of the target type, is given by Fairley.¹¹⁷ The fragility of the erythrocytes was decreased. Some degree

115 Wintrobe, M. M., Matthews, E., Pollock, R., and Dobyns, B. M. A Familial Hemopoietic Disorder in Italian Adolescents and Adults, Resembling Mediterranean Disease (Thalassemia), *J. A. M. A.* **114** 1530 (April 20) 1940.

116 Dameshek, W. "Target Cell" Anemia. Anerythroblastic Type of Cooley's Erythroblastic Anemia, *Am. J. M. Sc.* **200** 445, 1940.

117 Fairley, N. H. A Peculiar Haemolytic Hypochromic Anaemia Associated with Post-Malarial Splenomegaly of Banti's Type, *Tr. Roy. Soc. Trop. Med. & Hyg.* **34** 173, 1940.

of hemopoietic response was obtained after the intramuscular injection of crude liver extract supplemented by the oral administration of medicinal iron, although the use, in conjunction, of refined concentrated liver extract and iron had been of no value. Splenectomy was followed by an exacerbation of the anemia. No hemolysins were demonstrated in the blood of this patient. The author suggests that the hemolytic process was due to the "escape of an intracellular lytic enzyme into the blood stream from pathological reticulo-endothelium following prolonged chronic malarial infection."

BANTI'S SYNDROME

During 1940 there appeared several important contributions to the understanding of the pathogenesis of the disorder described by Banti as splenic anemia. Thompson¹¹⁸ and Rousselot¹¹⁹ report conclusions arrived at during the observation of 137 cases of this disorder encountered in ten years at the spleen clinic of the Presbyterian Hospital, New York. Only the general conclusions of these authors can be given here, and the reader is referred to the original articles for the evidence on which they are based. Thompson and Rousselot deny the validity of the classic concept of the course of Banti's disease—a primary splenic enlargement progressing through stages of anemia, leukopenia and susceptibility to hemorrhage from varices and terminating in hepatic cirrhosis. They find evidence of portal vein hypertension in all cases of this disorder, and they attribute the splenomegaly, collateral circulation and esophageal varices to a difference between the portal and the peripheral venous pressure. Portal vein hypertension, according to them, may arise from a variety of demonstrable mechanical causes, which may be intrahepatic or extrahepatic. Rousselot states that in "cases of congestive splenomegaly due to extrahepatic obstructive lesions, the prognosis and variations in clinical behavior are dependent on two factors (1) the site of the obstructive lesion and (2) variants in the anatomy of the venous pattern."

Ravenna¹²⁰ agrees with the aforementioned authors in attributing Banti's splenomegaly to splenic congestion, but he states that the congestion is not dependent on an obstructive factor in the portal venous bed. In his opinion, it is due to primary lesions of the small splenic

118 Thompson, W. P. The Pathogenesis of Banti's Disease, *Ann Int Med* **14** 255, 1940

119 Rousselot, L. M. The Late Phase of Congestive Splenomegaly (Banti's Syndrome) with Hematemesis but Without Cirrhosis of the Liver. Further Observations on Etiology of Banti's Syndrome and Effect on Prognosis of Certain Variations in Portal Venous Pattern, *Surgery* **8** 34, 1940

120 Ravenna, P. Banti Syndrome (Fibrocongestive Splenomegaly). Definition, Classification and Pathogenesis, *Arch Int Med* **66** 879 (Oct) 1940

arteries, which regulate the blood flow into the spleen. He describes the spleen as an elastic rather than a contractile organ and as an automatic controller which regulates the pressure of the splenic venous blood and the amount of blood which can be discharged through the hepatic resistance. Congestive splenic enlargement is, therefore, according to this author, a mechanism to counterbalance either an increased volume of portal blood or an increased peripheral resistance to the discharge of a normal amount of blood. Splenic changes in Banti's disease he attributes to the lesions of the splenic arterioles, the regulatory power of which becomes insufficient to control the inflow of blood. The consequent congestive splenomegaly is the cause of the circulatory disturbance in the portal bed. Secondly, hepatic cirrhosis and venous thrombosis may aggravate the disordered state of the portal circulation.

Herliky¹²¹ reports the case of a woman aged 30, believed to have Banti's disease, who suffered repeated hematemeses before the development of splenomegaly. Wentz and Kato¹²² observed a 6 year old girl with progressive splenomegaly, anemia, leukopenia, gastric hemorrhage, terminal jaundice and ascites. Necropsy revealed primary carcinoma of the liver.

Observations on the value of splenectomy in the treatment of Banti's disease have been published by Barg and Dulin¹²³. Of 43 patients seen during an eighteen year period, splenectomy was performed on 22, with an operative mortality of 27 per cent. The group of surgically treated patients is not entirely comparable to the group not given surgical treatment, and the criteria on which the decision in favor of splenectomy was based are not stated. The average age of the surgically treated patients was 35 years, and that of patients on whom no operation was performed was 43 years. The authors feel that duration of life was prolonged by splenectomy, although it is doubtful if the data presented support this conclusion.

POLYCYTHAEMIA VERA

Graham,¹²⁴ in reviewing some of Osler's early publications, commented on his fundamental understanding of the clinical aspects, as well as the pathologic physiology, of polycythaemia vera. Osler expressed the opinion that the symptoms and signs which characterize the disease

121 Herliky, J. D. Repeated Haematemeses Associated with Banti's Disease of "Conceded" Type, *M. J. Australia* **2** 759, 1939.

122 Wentz, V. B., and Kato, K. Primary Carcinoma of the Liver, with Banti's Syndrome, *J. Pediat* **17** 155, 1940.

123 Barg, E. H., and Dulin, J. W. Splenectomy in the Treatment of Banti's Syndrome, *Arch. Surg* **41** 91 (July) 1940.

124 Graham, D. Erythraemia-Polycythaemia Rubra Vera, *Canad. M. A. J.* **42** 281, 1940.

were due to increased viscosity of the blood and to decreased blood flow. Compensatory erythremia, which is often difficult to differentiate from true polycythemia, may, according to Hallock,¹²⁵ be distinguished on the basis of the blood volume, the red cell mass and the plasma volume. The figures for these quantities were all higher in persons with polycythemia vera than in normal persons. In those with erythremia related to congenital heart disease, although the red cell mass and the total blood volume were increased, the plasma volume per kilogram of body weight was decreased. Hallock interpreted these results as indicating that the increased red cell volume is a compensatory mechanism to maintain blood volume and oxidation. Bassen and Abel¹⁻⁶ described several cases of pseudopolycythemia due to dehydration. They also emphasized the importance of determining the cell mass for diagnostic purposes. In addition, they pointed out that obesity rarely occurs in cases of polycythemia vera.

Although polycythemia is rather uncommon, Dameshek and Henstell¹²⁷ suggested that it occurs more often than is suspected and that the apparent rarity is due in part to lack of recognition. They feel that the disease may masquerade for years and that to make the diagnosis it is necessary to take a careful history and to make a thorough physical examination and complete laboratory studies. Dameshek and Henstell describe several cases of polycythemia vera, with many different outstanding symptoms, and classify them according to the systems involved. In analyzing their group of cases, the authors noted that symptoms due to disease of the central nervous system predominated. Other common symptoms were those due to involvement of the gastrointestinal tract and the cardiovascular system. The following signs are important: plethora of the face, purple lips, congested conjunctival blood vessels, red ears, beefy red hands and, less commonly, beefy red feet, distended retinal vessels, blue in color, purplish tongue, large and thickly coated, palpable liver and spleen, and an elevated blood pressure. The outstanding laboratory findings are increases in hemoglobin concentration, red cells, white cells (especially polymorphonuclear neutrophils), platelets and blood volume. The bone marrow shows generalized hyperplasia of all the elements (panmyelosis). In conclusion, Dameshek and Henstell suggest that the best form of treatment is phlebotomy and a non-poor diet.

125 Hallock, P. Polycythemia of Morbus Caeruleus (Cyanotic Type of Congenital Heart Disease), *Proc Soc Exper Biol & Med* **44** 11, 1940.

126 Bassen, F. A., and Abel, H. A. Pseudo-Polycythemia, *J Mt Sinai Hosp* **6** 322, 1940.

127 Dameshek, W., and Henstell, H. H. The Diagnosis of Polycythemia, *Ann Int Med* **13** 1360, 1940.

The peripheral vascular disturbances which occur in polycythemia are emphasized by Zeiter¹²⁸. He noted that the symptoms may be vague for several years and are remittent in type, though progressive. The vascular complications, which he observed in 29 per cent of the cases, usually occurred in older people. The author suggested several types of treatment, including the administration of acetylphenylhydrazine, roentgen irradiation, administration of arsenic and periodic phlebotomy, in order to maintain the red cell mass slightly below normal. Fetterman and Spitler¹²⁹ pointed out that among the many factors which may cause vascular disorders of the peripheral nerves, polycythaemia vera is not unusual. The symptoms in general are dependent on the nerve involved, the extent of the pathologic changes and the general status of the patient.

The therapy of polycythaemia vera is not specific and is often unsuccessful. Pierson and Smith¹³⁰ treated 5 patients with polycythemia by the spray method of roentgen irradiation. The detailed procedure is accurately described. In 4 cases remissions were obtained which lasted twenty-three, fourteen, ten and seven months, respectively. The authors condemn the use of acetylphenylhydrazine, as well as phlebotomy, and state that the spray method of roentgen therapy is most satisfactory. As mentioned previously, both Dameshek and Henstell¹²⁷ and Zeiter¹²⁸ recommend phlebotomy as the method of choice. Stenstrom and his co-workers¹³¹ treated 4 patients with polycythaemia vera by roentgen irradiation over the areas of the pylorus and Brunner's glands. No changes were observed in the peripheral blood, and it is the opinion of these investigators that this method has no value. In the "Conferences on Therapy" related to the treatment of the blood disorders,¹³² it was the consensus that radiation, acetylphenylhydrazine and solution of potassium arsenite U S P were beneficial but slow in action and should be used in conjunction with phlebotomy. Haden¹³³ states that the best method of treatment is phlebotomy.

128 Zeiter, W J. Peripheral Vascular Disturbances in Polycythemia, *M Clin North America* **24** 485, 1940

129 Fetterman, J L, and Spitler, D K. Vascular Disorders of Peripheral Nerves, *J A M A* **114** 2275 (June 8) 1940

130 Pierson, J W, and Smith, C D. Treatment of Polycythemia Vera by Roentgen Irradiation of Entire Body, *Am J Roentgenol* **43** 577, 1940

131 Stenstrom, K W, Hallock, P H, and Watson, C J. Negative Results of Irradiation Therapy of the Pylorus and Brunner's Gland Area in Patients with Polycythemia Vera, *Am J M Sc* **199** 646, 1940

132 Conferences on Therapy. The Treatment of Blood Disorders, Polycythemia, Hodgkin's Disease and Splenic Disorders, *J A M A* **115** 297 (July 27) 1940

133 Haden, R L. Treatment of Polycythemia Vera, *Cleveland Clin Quart* **7** 166, 1940

Many interesting animal experiments concerned with the etiologic factors in polycythemia have been performed. Adamson and Storey¹³⁴ injected into rats (maintained on a milk diet) gastric juice obtained from patients with various blood dyscrasias. They noted an increase in reticulocytes after the injection of normal gastric juice and an added response after stimulation with histamine. Injections of gastric juice from patients with pernicious anemia induced no such response. Histamine alone produced a reticulocyte response. When gastric juice obtained from a patient with polycythemia was injected, a maximum reticulocyte response occurred, with no subsequent increase following the administration of histamine. The authors conclude from these results that patients with polycythemia may have an excess of histamine, which produces the high red cell count, or they may be sensitive to the drug.

The relationship between polycythemia and tumors in rats was investigated by Allen.¹³⁵ Polycythemia was produced and maintained by multiple transfusions. The author concludes that polycythemia *per se* does not inhibit tumor growth and that the changes which occurred in the tumors were due to congestion.

Brewer¹³⁶ made a statistical study of cobalt polycythemia in dogs. He noted no symptoms in his animals for at least one month with doses as high as 30 mg per day per kilogram of body weight. If the cobalt was increased to 50 mg daily, symptoms occurred in two weeks. The hemoglobin content was increased with daily amounts of 5 mg, the red blood cell count increased on a daily dose of 10 mg, and the hematocrit reading was altered after somewhat larger doses.

Factors affecting the maintenance of cobalt polycythemia in rats were studied by Anderson and his colleagues.¹³⁷ They noted that daily fluctuations in counts could be eliminated if they severed the lateral vein of the tail of the rat instead of cutting off the tip when drawing samples of blood, thus eliminating the disturbing factor of hemorrhage. Employing this technique, the authors noted that when whole liver, powdered liver extract or pernicious anemia concentrate was added to the basic milk diet a higher level of red cells was produced and maintained. They further observed that casein had only a slight effect and liver residue none. If the calcium-phosphorus ratio was reduced to 0.6 by

134 Adamson, W. B., and Storey, J. E. Observations on the Etiology of Polycythemia Vera, *Texas State J. Med.* **36** 26, 1940.

135 Allen, F. M. Transfusions and Polycythemia in Normal and Tumor-Bearing Rats, *J. Lab. & Clin. Med.* **25** 471, 1940.

136 Brewer, G. A Statistical Study of Cobalt Polycythemia in Dog, *Am. J. Physiol.* **128** 345, 1940.

137 Anderson, H. D., Underwood, E. J., and Elvehjem, C. A. Factors Affecting the Maintenance of Cobalt Polycythemia in Rat, *Am. J. Physiol.* **130** 373, 1940.

the addition of sodium biphosphate (NaH_2PO_4), the rate of development of polycythemia increased, the cobalt was more toxic and there was a depression of growth

The mechanism of development of cobalt polycythemia in dogs was also investigated by Davis¹³⁸ He noted that the combination of cobalt and anoxia had an added effect in producing polycythemia The addition of ascorbic acid to the diets depressed development of the cobalt polycythemia, but not that of the anoxia type In animals with cobalt polycythemia the ascorbic acid content of the blood was diminished The author believes that cobalt produces polycythemia by interfering with the respiratory function of vitamin C, hence stimulating erythropoiesis In conclusion, the author points out that cobalt administered in small amounts over a long period will produce polycythemia without any other toxic effects

BLOOD COAGULATION

Hemorrhagic Disorders Related to Prothrombin Deficiency—Vitamin K and Prothrombin Of the many functions and properties of the blood, that of coagulation is unique in being devoted primarily to the preservation of the blood itself The several factors and their complex relationships concerned with the process of coagulation continue to engage the interest of chemists, physiologists and clinical investigators Of the nature of such factors and the conditions which may predispose to or condition their aberration, greatest knowledge in recent years has been acquired with respect to prothrombin Investigations dealing with prothrombin and with the role of vitamin K in its production have been devoted to varied aspects of the problem chemical studies of natural and synthetic substances possessing vitamin K activity, the biologic assay of such materials and the standardization of methods of assay, procedures for the estimation of the effective prothrombin of whole blood or plasma, the experimental production and amelioration of vitamin K and prothrombin deficiencies, recognition of such deficiency states in man and the factors responsible for them, and, finally, adaptation of the information acquired by such studies to the correction of hemorrhagic disease or to lessening the risk of uncontrollable bleeding in man We shall not attempt to discuss the contributions to the chemical knowledge of vitamin K made during the past year For a complete review the reader is referred to the annotated bibliography of vitamin K published by Merck & Co, Inc¹³⁹

138 Davis, J E The Effect of Ascorbic Acid Administration upon Experimental Polycythemia The Mechanism of Cobalt Polycythemia, *Am J Physiol* **129** 140, 1940

139 Vitamin K Annotated Bibliography, Rahway, N J, Merck & Co, Inc, June 1940

The results of a detailed study of the rate at which the plasma prothrombin level falls when newly hatched chicks are placed on a vitamin K-deficient diet are reported by Tidrick and associates¹⁴⁰. They observed prolongation of the clotting time of whole blood when the prothrombin fell to about 30 per cent of the normal level for control chicks. Hemorrhages occurred at a level approximately 10 per cent of normal. Large doses of 2-methyl-1,4-naphthoquinone^{140a} corrected the deficit almost completely within six hours. Using chick methods of assay, Ansbacher¹⁴¹ concluded that vitamin K₁ (2-methyl-3-phytyl-1,4-naphthoquinone) and other phytyl derivatives of methylnaphthoquinone were not as active and not as readily utilized by the animal body as 2-methyl-1,4-naphthoquinone. Ansbacher and his colleagues¹⁴² also came to the conclusion that the water-soluble substances methylnaphthoquinone and methylnaphthohydroquinone are the most active vitamin K compounds known at present. Thayer and his associates,¹⁴³ using a six hour chick assay method, record the activity of 2-methyl-3-phytyl-1,4-naphthoquinone as about one-half that of 2-methyl-1,4-naphthoquinone and thereby disagree with the statements of Ansbacher that the difference in activity of the two compounds approximates 1:30. Richert and his associates¹⁴⁴ determined by bioassay methods the activity of various water-soluble antihemorrhagic compounds administered intravenously. On a molecular basis all were approximately equal to the standard, 2-methyl-1,4-naphthoquinone, with the exception of dipotassium-1,4-dihydroxy-2-methylnaphthalene disulfate, which was distinctly less active.

A new method of preparing thromboplastin reagent from rabbit brain for the determination of prothrombin is described by Quick¹⁴⁵. An acetone extract is dehydrated rapidly and the desiccated material placed in glass ampules from which the air is subsequently evacuated by means of an oil vacuum pump before the ampules are sealed in a flame.

140 Tidrick, R. T., Joyce, F. T., and Smith, H. P. Vitamin K Deficiency and Prothrombin Levels. Effect of Vitamin K Administration, *Proc Soc Exper Biol & Med* **42** 853, 1939.

140a This compound has recently been given the name menadione.

141 Ansbacher, S. Vitamin K, *J Biol Chem* **133** iii, 1940.

142 Ansbacher, S., Fernholz, E., and Dolliver, M. A. Water-Soluble Antihemorrhagic Compounds, *Proc Soc Exper Biol & Med* **43** 652, 1940.

143 Thayer, S. A., McKee, R. W., Binkley, S. B., and Doisy, E. A. Potencies of Vitamin K₁, and of 2-Methyl-1,4-Naphthoquinone, *Proc Soc Exper Biol & Med* **44** 585, 1940.

144 Richert, D., Thayer, S. A., McKee, R. W., Binkley, S. B., and Doisy, E. A. Bioassay of Water-Soluble Antihemorrhagic Compounds by Intravenous Administration, *Proc Soc Exper Biol & Med* **44** 601, 1940.

145 Quick, A. J. The Thromboplastin Reagent for the Determination of Prothrombin, *Science* **92** 113, 1940.

Dehydration of rabbit brain by acetone or by dioxane (diethylene dioxide) markedly increases the thromboplastic activity of the substance. In the sealed evacuated ampules the material apparently retains its potency indefinitely. Souter, Kark and Taylor¹⁴⁶ have employed "lyophilized" extract of dried whole rabbit brain, stored in evacuated containers, as a stable source of thromboplastin. These authors advocate the use of dried whole brain, rather than acetone-extracted brain, for thromboplastic activity, since the extreme potency of the latter material may prevent recognition of changes in prothrombin time until the content of prothrombin is considerably decreased.

A number of biologic materials other than tissue extracts exhibit thromboplastic activity. Among these are the venoms of certain snakes. Fullerton¹⁴⁷ has made successful use of venom from Russell's viper for this purpose. The procedure employed is identical with that of Quick except for the substitution of 0.1 cc of the venom solution for rabbit brain extract. One-tenth milligram of the dried venom, available commercially, is dissolved in 1 cc of distilled water. In the desiccated state the material retains its potency for several months.

Kaump and Greenwood¹⁴⁸ report that the Quick method for determination of prothrombin time gave best results in their hands when the constituents were used in the relative proportions of solution of calcium chloride 25 per cent, suspension of thromboplastin 25 per cent and plasma 50 per cent. The quantities employed were, respectively, 0.25, 0.25 and 0.5 cc. Of the extracts of various tissues tested none was superior to rabbit brain as a source of thromboplastin. Kato¹⁴⁹ has devised a modification of Quick's method using 10 cu mm of oxalated whole blood. The average normal value for the prothrombin time, by this procedure, is given as 20 ± 2 seconds. A one stage method utilizing serial dilutions of oxalated plasma, with the addition of thromboplastin in the form of beef lung extract, and solution of calcium chloride is described by Allen, Julian and Dragstedt¹⁵⁰. They observed that a 35

146 Souter, A. W., Kark, R., and Taylor, F. H. L. A Stable Thromboplastin for Use in Quick's Prothrombin Test, *Science* **91** 532, 1940. Souter, A. W., and Kark, R. Quick's Prothrombin Test Simplified by the Use of a Stable Thromboplastin, *Am J M Sc* **200** 603, 1940.

147 Fullerton, H. W. Estimation of Prothrombin. A Simplified Method, *Lancet* **2** 195, 1940.

148 Kaump, D. H., and Greenwood, J. H. Plasma Prothrombin Determination, *Am J Clin Path* **10** 397, 1940.

149 Kato, K. Microprothrombin Test with Capillary Whole Blood. Modification of Quick's Quantitative Method, *Am J Clin Path* **10** 147, 1940.

150 Allen, J. G., Julian, O. C., and Dragstedt, L. R. Use of Serial Dilutions in Determination of Prothrombin by the One Stage Technic, *Arch Surg* **41** 873 (Oct) 1940.

per cent dilution of normal plasma was required before a change in the clotting time occurred. The dilution technic was found especially valuable in cases of delayed response to administration of vitamin K, such as may be shown by patients with nontropical sprue. In the plasma of a patient suffering with serum sickness a substance inhibiting the prothrombin-thrombin reaction was detected. Ziffren and co-workers¹⁵¹ have published the details of a simple one stage method of measuring approximately the prothrombin content of whole blood. A modification of Howell's method for determination of prothrombin time is announced by Cheney¹⁵². Various amounts of solution of calcium chloride are mixed with oxalated plasma to which no thromboplastin has been added. A plasma dilution method for the estimation of prothrombin is reported by Thordarson¹⁵³. Highly dilute oxalated plasma is added to a solution containing fibrinogen, thromboplastin, calcium and buffer salts. The clotting times of a range of dilutions of the patient's plasma are compared with those obtained with a standard prothrombin solution. The latter consists of the author's oxalated plasma, which is assumed to remain essentially unchanged with respect to prothrombin content. The method appears to have merit but is probably too time consuming to secure wide acceptance.

Warner and Flynn,¹⁵⁴ using the Warner, Binkhous and Smith procedure for determination of prothrombin and employing rats suffering with a nutritional deficiency of vitamin K, observed that the addition of bile salts failed to modify appreciably the therapeutic efficacy of the water-soluble potassium salt of the disulfuric acid ester of 2-methyl-1,4-naphthoquinone. Elliott, Isaacs and Ivy¹⁵⁵ induced prothrombin deficiency in rats by the addition of 20 per cent by weight of liquid petrolatum to a diet which in other respects was similar to the diet of control animals. Vitamin K, administered subcutaneously, corrected the deficiency, supplementary vitamin D (viosterol in oil) was said to improve it, but the administration of vitamin A had no apparent effect.

151 Ziffren, S. E., Owen, C. A., Hoffman, G. R., and Smith, H. P. A Simple Bedside Test for Control of Vitamin K Therapy, *Am J Clin Path (Tech Supp)* **4** 13, 1940.

152 Cheney, G. The Plasma Coagulation Time as a Simple Test for Vitamin K Deficiency, *Am J M Sc* **200** 327, 1940.

153 Thordarson, O. A Method for Quantitative Determination of Prothrombin in Plasma, *Acta med Scandinav* **104** 291, 1940.

154 Warner, E. D., and Flynn, J. E. Absorption of Water-Soluble Vitamin K from Intestinal Tract, *Proc Soc Exper Biol & Med* **44** 607, 1940.

155 Elliott, M. C., Isaacs, B., and Ivy, A. C. Production of "Prothrombin Deficiency" and Response to Vitamins A, D and K, *Proc Soc Exper Biol & Med* **43** 240, 1940.

Prothrombin deficiency in rats was induced by Flynn and Warner¹⁵⁶ by means of biliary ligation and diet regulation. The potency of phthiocol (2-methyl-3-hydroxy-1,4-naphthoquinone) and 2-methyl-1,4-naphthoquinone in correcting the condition was determined by intraperitoneal and by intravenous injection of these drugs.

Andrus, Lord and Kauer¹⁵⁷ observed that in dogs the level of the plasma prothrombin was lower in blood returning from the lungs than in that obtained from the arterial side of the pulmonary circulation. Differences in oxygen content of the blood were not responsible. The authors consider this difference evidence of pulmonary removal of prothrombin. Lord, Andrus and Moore,¹⁵⁸ using the Warner, Binkhous and Smith technic for prothrombin estimation, determined by a curative assay method the vitamin K content of the livers of dogs subjected to various experimental procedures. They formulated a number of conclusions, based in part on their observations during the course of these studies. The authors state that in the formation of plasma prothrombin there enter an extrinsic factor (vitamin K), an intrinsic factor (bile salts), an absorptive mechanism (the intestinal epithelium) and an organ which stores vitamin K and elaborates plasma prothrombin (the liver). They draw an analogy between the mechanism involved in this process and that concerned with the formation of the erythrocyte-maturing factor. These authors reach the following conclusions: 1 Bile must reach the intestinal tract in order that absorption of fat-soluble vitamin K may occur, and the active constituents of the biliary secretion are the bile salts. 2 In dogs with obstructive jaundice or biliary fistula administration of bile salts alone does not suffice to prevent a fall in the plasma prothrombin. 3 Vitamin K is stored in the liver, and partial loss of the liver's supply is reflected in a linear manner by a corresponding decline in the prothrombin level. 4 The liver is the site of formation of plasma prothrombin, and for it to fulfil this function efficiently it must be healthy. 5 Prothrombin is constantly leaving the circulation, probably in the lungs. 6 The critical level of the plasma prothrombin with respect to hemorrhage is approximately 20 per cent of the normal value, as determined by the method employed.

Damage to the liver was caused in rats by poisoning with carbon tetrachloride, report Bollman, Butt and Snell¹⁵⁹. The extent of hepatic

156 Flynn, J. E., and Warner, E. D. Prothrombin Levels and Synthetic Vitamin K in Obstructive Jaundice of Rats, *Proc. Soc. Exper. Biol. & Med.* **43** 190, 1940.

157 Andrus, W. De W., Lord, J. W., Jr., and Kauer, J. T. Studies on the Fate of Plasma Prothrombin, *Science* **91** 48, 1940.

158 Lord, J. W., Jr., Andrus, W. De W., and Moore, R. A. Metabolism of Vitamin K and Role of the Liver in Production of Prothrombin in Animals, *Arch. Surg.* **41** 585 (Sept.) 1940.

159 Bollman, J. L., Butt, H. R., and Snell, A. M. The Influence of the Liver on the Utilization of Vitamin K, *J. A. M. A.* **115** 1087 (Sept. 28) 1940.

necrosis was greatest in animals fed a high fat diet and least in those with a high carbohydrate intake. Maximum regeneration occurred when a high protein diet was given. Hypoprote thrombinemia developed in all the animals whose livers were damaged, and the level of the prothrombin could not be correlated with the type of diet received. The heparin content and the antithrombin activity of the plasma were not greatly affected by necrosis of the liver. No effect on the prothrombin levels of these experimental rats was observed after the administration of natural or synthetic vitamin K.

Injury to the liver was produced in dogs by Brinkhous and Warner¹⁶⁰ by the repeated administration of small doses of chloroform. The ensuing hypoprote thrombinemia was not influenced by treatment with natural vitamin K and bile salts.

Kato and Poncher¹⁶¹ point out that Whipple,¹⁶² in 1912, recorded observations leading him to the conclusion that a deficiency of prothrombin was responsible for fatal hemorrhage in the newborn. By means of Kato's whole blood micromethod they determined the prothrombin time of 173 newborn infants. The subjects were classified as mature or premature on the basis of a body weight of 2,500 Gm at birth. The average prothrombin time of 100 mature infants estimated on the day of birth was forty-three and two-tenths seconds, and the corresponding value for the premature babies was forty-six and five-tenths seconds, whereas the average normal adult prothrombin time determined by this method is twenty seconds. The authors found no correlation between the extent of prothrombin deficiency, as measured on the first day of life, and the degree of immaturity. They advocate prothrombin time determinations on the blood of all newborn infants or, as a safeguard, routine administration of vitamin K to all mothers before confinement.

Bray and Kelley,¹⁶³ using a micromodification of Quick's method, determined the prothrombin time on 17 samples of cord blood and on the blood of 23 newborn infants during the first week of life. The clotting time of cord blood was usually low, and the readings obtained during the first day of life were in the adult range of normal values.

160 Brinkhous, K. M., and Warner, E. D. Effect of Vitamin K on Hypoprote thrombinemia of Experimental Liver Injury, *Proc Soc Exper Biol & Med* **44** 609, 1940.

161 Kato, K., and Poncher, H. G. The Prothrombin in the Blood of Newborn Mature and Immature Infants as Determined by the Microprothrombin Test, *J A M A* **114** 749 (March 2) 1940.

162 Whipple, G. H. Hemorrhagic Disease. Septicemia, Melena Neonatorum and Hepatic Cirrhosis, *Arch Int Med* **9** 365 (March) 1912, Hemorrhagic Disease. Antithrombin and Prothrombin Factors, *ibid* **12** 637 (Dec) 1913.

163 Bray, W. E., and Kelley, O. R. Prothrombin Studies, Especially in the Newborn, *Am J Clin Path* **10** 154 1940.

Thereafter the time increased to a maximum between the second and the fifth day and subsequently fell. The time was greatly prolonged in cases of hemorrhagic disease of the newborn. No correlation was found between the platelet count and the prothrombin level of the blood. Quick and Grossman¹⁶⁴ also observed normal prothrombin times at birth, with an abrupt increase during the first few days of life and subsequent spontaneous and prompt restoration of normal values. Absence of intestinal bacteria was considered responsible for vitamin K deficiency and the consequent fall in the prothrombin content of the plasma. They attributed hemorrhagic disease of the newborn to delayed restoration of the prothrombin level, a process which could be hastened by the oral administration of vitamin K. Salomonsen¹⁶⁵ likewise ascribes the hypoprothrombinemia of infancy to vitamin K deficiency dependent on a relatively sterile intestinal tract. He found that the administration of a little cow's milk periodically from the second hour of life prevented later disturbances of blood coagulation. Tocantins¹⁶⁶ observed a case of congenital atresia of the duodenum, with icterus and hemorrhagic manifestations, in a mulatto infant. Although the termination was fatal, the prothrombin time returned to normal spontaneously, and the bleeding ceased as the jaundice disappeared. Consequently, the author discards the theory attributing low prothrombin levels in infancy to lack of bacterial activity and suggests that the hypoprothrombinemia is due to incapacitation of the liver resulting from an excessive load of pigment from the breakdown of hemoglobin. An additional factor, he states, may be the abrupt termination of a supply of prothrombin from the placenta.

Nygaard¹⁶⁷ considers that inactivity of intestinal flora is but one factor in the causation of the transitory hypoprothrombinemia of the newborn and advises routine administration of vitamin K to women for a period of two weeks before expected confinement. He has used 2-methyl-1,4-naphthoquinone in a daily dose of 10 mg. Koller and Fiechter¹⁶⁸ found that giving vitamin K by mouth or by intramuscular

164 Quick, A. J., and Grossman, A. M. The Nature of the Hemorrhagic Disease of the Newborn. Delayed Restoration of the Prothrombin Time, *Am J M Sc* **199** 1, 1940

165 Salomonsen, L. Hemorrhagic Disease of Newborn, Due to Hypoprothrombinemia, *Nord med* **7** 1309, 1940

166 Tocantins, L. M. Probable Mechanism of the "Physiologic" Hypoprothrombinemia of the Newborn, *Am J Dis Child* **59** 1054 (May) 1940

167 Nygaard, K. K. Prothrombin Deficiency as Cause of Hemorrhagic Diathesis in the Newborn. Prophylaxis and Therapy with Vitamin K, *Nord med (Norsk mag f lægevidensk)* **7** 1535, 1940

168 Koller, F., and Fiechter, N. Die hamorrhagische Diathese des Neugeborenen und ihre Beziehung zum Vitamin K, *Schweiz med Wchnschr* **70** 136, 1940

injection from the first day of life prevented the rise in prothrombin time which occurs usually between the second and the sixth day. Case reports and analyses of plasma prothrombin values are given by Dam and his associates¹⁶⁹. In normal infants they found that a moderate vitamin K deficiency associated with hypoprothrombinemia develops during the first few days of life. Marked decrease of prothrombin was observed in cases falling under the clinical triad of hydrops foetalis, icterus gravis neonatorum and congenital anemia of the newborn. Increases in the plasma prothrombin content were demonstrated in 2 infants suffering with icterus gravis. Aside from its hemostatic effect, the use of vitamin K failed to influence the anemia.

The effects on the plasma prothrombin of infants exerted by various synthetic vitamin K compounds administered to the mother in labor were studied by Hellman, Moore and Shettles¹⁷⁰. Waddell, Guerry and Birdsong¹⁷¹ were able to prevent the development of hypoprothrombinemia in newborn infants by administration either of natural vitamin K orally during the first few days of life or of natural or synthetic vitamin K to the mother throughout the last two weeks of gestation. Snelling,¹⁷² using Quick's method, observed that the prothrombin time of cord blood was prolonged in many newborn infants, without associated evidence of hemorrhage. The daily administration of natural or synthetic vitamin K to prospective mothers had no effect on the maternal prothrombin time but shortened the time of coagulation of cord blood. He recommends the antepartum use of vitamin K in the prophylaxis of hemorrhagic disease of the newborn. Since orally administered vitamin K may not be retained or absorbed, the parenteral route is often preferable. Snelling reports that the intravenous use of 2-methyl-1,4-naphthoquinone lowers the prothrombin time of infants and is followed by cessation of bleeding in cases of hemorrhagic disease. The usual dose is 0.5 to 1.0 mg. in a fresh solution, not over one week old, and toxic effects have not been observed. The author recommends transfusion as a supplementary therapeutic measure in treating patients with low hemoglobin values.

169 Dam, H., Tage-Hansen, E., and Plum, P. Vitamin-K Lack in Normal and Sick Infants, *Lancet* **2** 1157, 1939.

170 Hellman, L. M., Moore, W. T., and Shettles, L. B. Factors Influencing Plasma Prothrombin in the New Born Infant. III. A Study of the Vitamin K Activity of Various Naphthohydroquinone Derivatives, *Bull. Johns Hopkins Hosp.* **66** 379, 1940.

171 Waddell, W. W., Jr., Guerry, D. P., III, and Birdsong, M. The Role of Vitamin K in the Etiology, Prevention and Treatment of Hypoprothrombinemia and the Hemorrhagic Diathesis of the Newborn, *South. M. J.* **33** 974, 1940.

172 Snelling, C. E. Vitamin K in Hemorrhagic Disease of the Newborn Infant, *J. Pediat.* **17** 615, 1940.

Low plasma prothrombin levels were found in 52 of 76 infants examined during the first eight days of life by Kove and Siegel¹⁷³. The average value was lowest during the first two days. Diet histories obtained from the mothers of 68 of the babies failed to reveal any correlation between the maternal dietary intake of vitamin K and the prothrombin values for the infants. However, such a correlation was established when medicinal vitamin K was taken by the mother before confinement. The authors advise routine antepartum administration of the vitamin. Waddell and Lawson¹⁷⁴ present evidence indicating that avitaminosis K and associated prothrombin deficiency may be an important factor in many cases of intracranial hemorrhage occurring during birth. The antepartum use of vitamin K is believed to be of value in preventing such accidents. The authors give the vitamin to all women before delivery, as well as to all infants during the first days of life. General discussions of vitamin K and hypoprothrombinemia with reference to pediatrics have been published by Grossman¹⁷⁵ and by Thompson¹⁷⁶.

The prothrombin content of the plasma during pregnancy has been studied by Thordarson¹⁷⁷. The level, he found, begins to increase at the third month of gestation and continues to rise until delivery. The prothrombin content of blood from normal nonpregnant women was expressed by an index of 100, in pregnant women at three months average values ranged between 111 and 123 and at six months between 146 and 149, while at nine months the average value was 169. Beginning on Sept. 1, 1939, Hellman, Shettles and Eastman¹⁷⁸ gave orally 2 mg. of 2-methyl-1,4-naphthoquinone to every other patient admitted in labor to the Johns Hopkins Hospital. In the control series of 392 subjects 16, or 4.1 per cent, of the deliveries resulted in stillbirths or neonatal deaths. The corresponding figure for the treated series, comprising 384 members, was 6, or 1.5 per cent. The probability is 6:1 against the difference being due to an error in sampling. According to the authors, review

173 Kove, S., and Siegel, H. Prothrombin in the Newborn Infant. Relationship to the Maternal Dietary Vitamin K Intake, *J. Pediat.* **17** 448, 1940.

174 Waddell, W. W., Jr., and Lawson, G. M. Hemorrhagic Diathesis of the Newborn. Further Observations Concerning Prevention and Treatment, *J. A. M. A.* **115** 1416 (Oct. 26) 1940.

175 Grossman, A. M. Vitamin K for the Pediatrician with Special Reference to Physiologic Hypoprothrombinemia of Newborn Infants, *J. Pediat.* **16** 239, 1940.

176 Thompson, W. H. Prothrombin Deficiency and Vitamin K in the Newborn Period, *J. Tennessee M. A.* **33** 218, 1940.

177 Thordarson, O. Hyperprothrombinaemia During Pregnancy, *Nature*, London **145** 305, 1940.

178 Hellman, L. M., Shettles, L. B., and Eastman, N. J. Vitamin K in Obstetrics. A Review of One Year's Experience, *Am. J. Obst. & Gynec.* **40** 844, 1940.

of the necropsy observations attaches still greater significance to the results. They recommend the routine antepartum administration of vitamin K. Fitzgerald and Webster¹⁷⁹ studied the effects of vitamin K given during labor. More than 100 women, including treated subjects and controls, were observed. No change in the maternal plasma prothrombin time occurred in patients who did not receive vitamin K. Administration during a period of one to twenty-four hours before delivery of either natural vitamin K by mouth or of 2 mg of 2-methyl-1,4-naphthoquinone by the intravenous route was followed by a rise in the prothrombin content of both the maternal and the cord blood. These workers observed a definite depression of the prothrombin level in both mother and child after the use of pentobarbital sodium as an analgesic during labor.

According to Weir, Butt and Snell,¹⁸⁰ factors important in the development of hypoprothrombinemia are inadequate intake of vitamin K or the substances necessary for its manufacture in the intestine, impairment of absorption of the vitamin and hepatic injury. Intravenous use of four synthetic compounds in clinical cases of hypoprothrombinemia were attended with excellent results, except in patients with disease of the liver. The intravenous method of administration possesses the advantages of precise dosage, instant availability and elimination of the variable factor of absorptive capacity. The rapidity of action of the drug suggested to the authors that it may function in an enzymatic manner.

The Ivy method for determination of bleeding time and the serum volume test of Boyce and McFetridge, with correction for anemia, were used by Ferguson and his associates¹⁸¹ for the estimation of the bleeding time in cases of jaundice. They report that either of these tests, or the combined application of the two, revealed the presence of a hemorrhagic tendency in every case of jaundice in which such a tendency was indicated by the results of the Quick method for determination of prothrombin time. Wilson¹⁸² determined the level of the plasma prothrombin in 41 patients without obstructive jaundice or biliary fistula and found a correlation between the values obtained and the results of the hippuric acid test of hepatic function. Clinical conditions

179 Fitzgerald, J. E., and Webster, A. Effect of Vitamin K Administered to Patients in Labor, *Am J Obst & Gynec* **40** 413, 1940.

180 Weir, J. F., Butt, H. R., and Snell, A. M. Further Observations on the Clinical Use of Vitamin K, *Am J Digest Dis* **7** 485, 1940.

181 Ferguson, L. H., Calder, D. G., Jr., and Reinhold, J. G. The Ivy Bleeding Time, Serum Volume Index and Prothrombin Content of Blood in Estimating Bleeding Tendency in Jaundice, *Surg, Gynec & Obst* **71** 603, 1940.

182 Wilson, S. J. Quantitative Prothrombin and Hippuric Acid Determinations as Sensitive Reflectors of Liver Damage in Human Subjects, *J Lab & Clin Med* **25** 1139, 1940.

studied included cirrhosis of the liver and various disorders of the blood. No correlation between the fibrinogen content of the plasma and the ability to synthesize and excrete hippuric acid was observed. The galactose tolerance test gave normal results for all of the subjects examined, whereas the degree of bromsulphalein retention varied widely. Cullen and his co-workers¹⁸³ report on a clinical study of changes of the plasma prothrombin level following anesthesia induced by various agents. Lowering of the prothrombin content followed administration of chloroform, whereas neither ether nor cyclopropane produced such an effect.

The existence of avitaminosis K and associated hypoprothrombinemia on an exclusive nutritional basis is still in controversy, but evidence is accumulating that dietary deficiency must be regarded at least as an important contributing factor in some cases of lowered plasma prothrombin. Eighteen cases in which there were associated clinical signs of various forms of avitaminosis, other than K, are reported by Scarborough¹⁸⁴. In none of these was prolongation of prothrombin time exhibited by the method of Quick. His results are at variance with those published by Kark and Lozner¹⁸⁵. They observed 4 patients, with evidence of avitaminosis and a history of dietary deficiency, in whom the prothrombin coagulation time was delayed. Hemorrhagic manifestations in these patients were attributed to lack of vitamin C rather than of vitamin K, but the prothrombin times were restored to normal after oral administration of vitamin K. None of the patients was jaundiced. Mackie¹⁸⁶ reports the results of prothrombin studies and the response to treatment of 277 patients with various disorders. Of these, 57 exhibited hypoprothrombinemia, by Quick's method, in the absence of jaundice or evidence of disease of the liver. Some patients improved with diet therapy alone, others responded to oral use of vitamin K without bile salts, one group was treated successfully with dehydroxycholic acid (obtainable as decholin) without vitamin K, and some patients required the two therapeutic agents in combination. Six members of the series exhibited severe hemorrhagic manifestations, and among these either absorptive difficulty or disease of the liver, rather

183 Cullen, S. C., Ziffren, S. E., Gibson, R. B., and Smith, H. P. Anesthesia and Liver Injury, with Special Reference to Plasma Prothrombin Levels, *J. A. M. A.* **115** 991 (Sept 21) 1940.

184 Scarborough, H. Nutritional Deficiency of Vitamin K in Man, *Lancet* **1** 1080, 1940.

185 Kark, R., and Lozner, E. L. Nutritional Deficiency of Vitamin K in Man. A Study of Four Non-Jaundiced Patients with Dietary Deficiency, *Lancet* **2** 1162, 1939.

186 Mackie, T. T. Vitamin K Deficiency in the Absence of Jaundice, *New York State J. Med.* **40** 987, 1940.

than dietary deficiency, was regarded as a chief cause of hypoprothrombinemia. Mason¹⁸⁷ observed normal plasma prothrombin levels in patients suffering with pernicious anemia, pellagra or spina who were receiving treatment with liver extract and vitamins.

The response of patients exhibiting lowered values for plasma prothrombin in association with biliary and hepatic disease to treatment with natural and synthetic vitamin K given by oral, intramuscular and parenteral routes has been the subject of numerous communications. It has been generally observed that vitamin K therapy is inefficacious in cases of severe hepatic disease, and at present this constitutes the only recognized condition in which the intravenous administration of potent synthetic vitamin K compounds is without effect. Several authors¹⁸⁸ comment on the information regarding hepatic function which may be afforded by a determination of prothrombin time and the degree of response to parenteral administration of vitamin K.

187 Mason, H. C. Normal and Abnormal Prothrombin Levels, *Proc Soc Exper Biol & Med* **44** 70, 1940.

188 Andrus, W. De W., and Lord, J. W., Jr. Clinical Investigations of Some Factors Causing Prothrombin Deficiencies. Significance of the Liver in Their Production and Correction, *Arch Surg* **41** 596 (Sept.) 1940, Use of Intramuscular Injections of 2-Methyl-1, 4-Naphthoquinone in Treatment of Prothrombin Deficiencies, with Note on Role of Liver in Response to This and Other Substances with Vitamin K Activity, *Ann Surg* **112** 783, 1940. Pohle, F. J., and Stewart, J. K. Observations on the Plasma Prothrombin and the Effects of Vitamin K in Patients with Liver or Biliary Tract Disease, *J Clin Investigation* **19** 365, 1940. Allen, J. G., and Julian, O. C. Response of Plasma Prothrombin to Vitamin K Substitute Therapy in Cases of Hepatic Disease, *Arch Surg* **41** 1363 (Dec.) 1940. Cheney, G. Vitamin K Deficiency in a Case of Gall Bladder Disease Without Clinical Jaundice or Hepatitis, *Am J Digest Dis* **7** 521, 1940. Townsend, S. R., and Mills, E. S. Haemorrhagic Tendency Associated with Prothrombin Deficiency and Its Treatment with Vitamin K and Bile, *Canad M A J* **42** 541, 1940. Rhoads, J. E., and Fliegelman, M. T. The Use of 2-Methyl-1, 4-Naphthoquinone (a Synthetic Vitamin K Substitute) in the Treatment of Prothrombin Deficiency in Patients, *J A M A* **114** 400 (Feb. 3) 1940. Aggeler, P. M., Lucia, S. P., and Goldman, L. Effect of Synthetic Vitamin K Compounds on Prothrombin Concentration in Man, *Proc Soc Exper Biol & Med* **43** 689, 1940. Macfie, J. M., Bacharach, A. L., and Chance, M. R. A. The Vitamin K Activity of 2-Methyl-1, 4-Naphthoquinone and Its Clinical Use in Obstructive Jaundice, *Brit M J* **2** 1220, 1939. Butt, H. R., Snell, A. M., Osterberg, A. E., and Bollman, J. L. Treatment of Hypoprothrombinemia. Use of Various Synthetic Compounds Exhibiting Anti-Hemorrhagic Activity (Vitamin K₁ Activity), *Proc Staff Meet, Mayo Clin* **15** 69, 1940. Andrus, W. De W., and Lord, J. W., Jr. Correction of Prothrombin Deficiencies by Means of 2-Methyl-1, 4-Naphthoquinone Injected Intramuscularly, *J A M A* **114** 1336 (April 6) 1940. Kark, R., and Souter, A. W. Synthetic Vitamin K in the Treatment of Hypoprothrombinaemia, *Lancet* **1** 1149, 1940. Norcross, J. W., and McFarland, M. D. Intravenous Use of 2-Methyl-1, 4-Naphthoquinone in Hypoprothrombinemia. Clinical Observations, *J A M A* **115** 2156 (Dec. 21) 1940.

Because of the increasing use of "banked" blood for transfusions, interest has been shown in the effects of storage on the prothrombin content of such blood. Quick¹⁸⁹ observed a significant decrease in prothrombin occurring within two days of removal of blood. Reinhold, Valentine and Ferguson¹⁹⁰ report that 73 per cent or more of the original prothrombin content of stored blood is present up to three days, after seven days of storage the majority of samples of blood possess less than half of their original prothrombin. Warner, DeGowin and Seegers¹⁹¹ noted a gradual decrease in the prothrombin content of preserved blood, amounting to about 50 per cent of the original level after three weeks of storage. However, they found that at the end of ten days most blood retained 90 per cent of its prothrombin activity. The use of either a solution of citrate alone or a solution of dextrose and citrate as an anticoagulant and preserving agent made no difference in the rate of prothrombin loss. Ziegler, Osterberg and Hovig¹⁹² report a 60 per cent loss of prothrombin content after three weeks of storage, but only a 10 to 20 per cent decrease after eight days.

Several general articles on the role of vitamin K and prothrombin in hemorrhagic disorders have appeared in the past year.¹⁹³ An extensive and detailed review of the entire subject, embodying the literature which appeared up to and including 1939, has been published by Brinkhous.¹⁹⁴

Factors in Blood Coagulation Other Than Vitamin K and Prothrombin—A résumé and recapitulation of his observations and views on the mechanism of blood clotting have been published by Ferguson.¹⁹⁵ According to this author, coagulation is explained in part by the formation of an intermediary colloidal complex containing prothrombin, cephalin and calcium in definite quantitative proportions. "Ripe"

189 Quick, A. J. Prothrombin in Preserved Blood, *J. A. M. A.* **114** 1342 (April 6) 1940.

190 Reinhold, J. G., Valentine, E. H., and Ferguson, L. K. The Effect of Storage on the Prothrombin Content of Citrated Blood, *Am. J. M. Sc.* **199** 774, 1940.

191 Warner, E. D., DeGowin, E. L., and Seegers, W. H. Studies on Preserved Human Blood. Decrease in Prothrombin Titer During Storage, *Proc. Soc. Exper. Biol. & Med.* **43** 251, 1940.

192 Ziegler, E. R., Osterberg, A. E., and Hovig, M. The Prothrombin Changes in Banked Blood, *J. A. M. A.* **114** 1341 (April 6) 1940.

193 Larson, C. P. The Present Status of Vitamin K, *West. J. Surg.* **48** 352, 1940. Greer, A. E. The Place of Vitamin K in Hemorrhagic Diseases, *Texas State J. Med.* **36** 218, 1940. Vitamin K and Cholemic Bleeding, editorial, *J. A. M. A.* **116** 143 (Jan 11) 1941.

194 Brinkhous, K. M. Plasma Prothrombin. Vitamin K, *Medicine* **19** 329, 1940.

195 Ferguson, J. H. The Role of Blood Clotting Anomalies in the Hemorrhagic Diseases, *J. Lab. & Clin. Med.* **26** 52, 1940.

thrombin can be prepared free from calcium. Prolongation of the clotting time may contribute to the development of those hemorrhagic states in which there can be demonstrated or postulated either deficiency of thromboplastin or prothrombin or excess of antithrombic factors. Calcium, according to Ferguson, may be excluded from practical consideration. Factors such as fibrinogen and platelet defects play their part in determining the effectiveness of coagulation and thrombosis in the arrest of hemorrhage. These, he considers, are all controlling or immediate mechanisms, and the prior causative factors, including capillary injury, must also receive consideration.

Views on the clotting mechanism in some respects at variance with those of Ferguson are expressed by Quick¹⁹⁶. He believes that calcium is already bound to prothrombin before its reaction with thromboplastin and that ionized calcium takes no part in the transformation of prothrombin to thrombin. The prothrombin-calcium combination, in Quick's opinion, is identical with Ferguson's intermediary complex. His conclusions are based, in part, on results of experiments with chicken blood, without the use of anticoagulant but with an excess of thromboplastin. The studies were so designed that calcium would be the only variable factor present.

Based on the coagulation theory first expounded by Morawitz in 1908, and later developed by Howell, Quick¹⁹⁷ has published a clinical classification of hemorrhagic diseases. Other general discussions of disturbances of blood coagulation and their clinical manifestation are given by Heck¹⁹⁸ and Sanford¹⁹⁹.

Inactivation of the thrombin of beef plasma by treatment with human or beef plasma or horse serum is reported by Stewart and Rourke²⁰⁰. The thrombin was not inactivated by a solution of fibrinogen. A component of the albumin fraction of the plasma is believed responsible for the inactivating effect. A method is described by Wilson²⁰¹ for the quantitative determination of the antithrombic activity of serum and plasma, and the unit of antithrombin is defined as that amount which

196 Quick, A. J. Calcium in the Coagulation of the Blood, *Am J Physiol* **131** 455, 1940.

197 Quick, A. J. Classification of Hemorrhagic Diseases Due to Defects in the Coagulation Mechanism of the Blood, Based on Recently Published Studies, *Am J M Sc* **199** 118, 1940.

198 Heck, F. J. The Differential Diagnosis of Diseases with Hemorrhagic Manifestations, *Texas State J Med* **36** 536, 1940.

199 Sanford, H. M. Studies in Blood Coagulation Disturbances, *J Missouri M A* **37** 409, 1940.

200 Stewart, J. D., and Rourke, G. M. On the Inactivation of Thrombin by Plasma Protein, *J Clin Investigation* **19** 695, 1940.

201 Wilson, S. J. Quantitative Studies on Antithrombin, *Proc Soc Exper Biol & Med* **43** 676, 1940.

will inactivate or neutralize 1 unit of thrombin during four minutes' incubation at 28 C Solandt and Best²⁰² report studies on the influence of heparin on the coagulation mechanism and state that a single dose of heparin sufficient to raise the clotting time of the blood of an anesthetized dog to over six hours did not prevent the agglutination of platelets in the presence of a maximal stimulus With larger doses of heparin the effect on platelet agglutination, unlike that on the clotting time, took fifteen to fifty minutes to develop

Seventeen commercially available products with claimed thromboplastic activity and ten solutions of thromboplastin obtained from various species were tested by Aggeler and Lucia²⁰³ for their influence on coagulation of plasma from normal human subjects and plasma from subjects with hemophilia Commercial preparations designed for parenteral use exhibited no effect on the clotting times of the plasma tested Only products suitable for local or oral use were found to possess activity

Lozner, Jolliffe and Taylor²⁰⁴ report the case of a Negro with generalized tuberculous lymphadenitis and prolonged coagulation time The clotting defect was not like that present in persons with hemophilia, and anticoagulant activity toward normal blood was demonstrated in the patient's plasma

Forty-four patients in whom hematemesis or melena had occurred, for the most part associated with peptic ulcer, were studied by Moss, Schiff, Stevens and Rich²⁰⁵ Ascorbic acid levels of the plasma were determined and frequently were found to be low in cases of ulcer, although no etiologic significance with respect to hemorrhage was attached to this observation It was found that the bleeding time, estimated by the Ivy method, may be prolonged and reduction of the level of serum calcium may occur in association with hematemesis from a variety of causes In these cases there was no prolongation of the prothrombin time and the bleeding time, determined by the Duke method, the fibrinogen content of the blood and the number of platelets were normal Examination of the sternal marrow revealed no abnormality other than active regeneration

202 Solandt, D Y, and Best, C H Time-Relations of Heparin Action on Blood-Clotting and Platelet Agglutination, *Lancet* **1** 1042, 1940

203 Aggeler, P M, and Lucia, S P The Potency of Blood Coagulating Substances Biologic Assay, *Am J M Sc* **199** 181, 1940

204 Lozner, E L, Jolliffe, L S, and Taylor, F H L Hemorrhagic Diathesis with Prolonged Coagulation Time Associated with a Circulating Anticoagulant, *Am J M Sc* **199** 318, 1940

205 Moss, H K, Schiff, L, Stevens, R J, and Rich, M L The Blood in Cases of Hematemesis and Melena with Reference to Factors Influencing Hemorrhage, *Am J Digest Dis* **7** 490, 1940

Calder and Kerby²⁰⁶ found nicotinic acid to be effective in promoting coagulation in patients suffering with brucellosis. They also observed its value in correcting clotting and bleeding defects in other toxic and infectious conditions. The effect of nicotinic acid was not identifiable with the action of calcium, thromboplastic material from platelets, prothrombin or thrombin. Experiments *in vitro* indicate that it may exert a neutralizing effect on antithrombin.

Extracts of shepherd's-purse and certain other plants were found by Steinberg, Segal and Parris²⁰⁷ to possess blood-coagulating activity. The oxalic acid content of the extracts was apparently largely responsible for their effect. The material was administered by intramuscular and intravenous injection in an effort to control hemorrhagic tendencies. The authors devised a "clotting unit" for the substance employed and obtained a large measure of success from its use in many apparently unrelated hemorrhagic disorders.

An experimental and clinical study of the effects of induced fever in promoting hemorrhage is reported by Wilson and Doan²⁰⁸. They observed that elevation of body temperature results in anoxia and in depletion of the liver glycogen, which leads to hepatic and megakaryocytic injury, with consequent decrease in the prothrombin content of the plasma and the number of platelets in the blood. A reduction of fibrinogen may also occur. The changes were reversible.

Hemorrhagic Disorders Other Than Those Related to Prothrombin Deficiency—Essential Thrombopenic Purpura. No important contributions have been made toward the solution of the problem of the mechanism of platelet deficiency and disturbed capillary integrity in essential purpura. Wiseman, Doan and Wilson,²⁰⁹ in a general article on this disorder, accompanied by case reports, favor excessive thrombocytolysis by an overactive spleen as the most probable cause of thrombopenia. They find no evidence of qualitative change in the megakaryocytes of the marrow. The authors recommend an attempt to sustain patients with this disease by medical measures, if possible, until a remission of activity occurs, but advocate splenectomy as a method of permanent cure in most cases. In their opinion, the more pronounced the bleeding the more urgent are the indications for removal of the spleen. An opposing view

206 Calder, R. M., and Kerby, G. P. The Effect of Nicotinic Acid on Blood Coagulation, *Am J M Sc* **200** 590, 1940.

207 Steinberg, A., Segal, H. I., and Parris, H. M. Role of Oxalic Acid and Certain Related Dicarboxylic Acids in Treatment and Control of Hemorrhage, *Ann Otol, Rhin & Laryng* **49** 1008, 1940.

208 Wilson, S. J., and Doan, C. A. The Pathogenesis of Hemorrhage in Artificially Induced Fever, *Ann Int Med* **13** 1214, 1940.

209 Wiseman, B. K., Doan, C. A., and Wilson, S. J. The Present Status of Thrombocytopenic Purpura, with Special Reference to Diagnosis and Treatment, *J A M A* **115** 8 (July 6) 1940.

regarding the mechanism of platelet decrease in essential purpura is expressed by Limaizi and Schleicher²¹⁰ They report studies of the peripheral blood and sternal marrow made on 29 subjects, including 5 normal men, 5 normal women and 7 patients with thrombopenic purpura in 2 of whom the condition was chronic The megakaryocytes of normal marrow are classified as young, adult and degenerated forms, on the basis of cytoplasmic changes with azule granulation Megakaryocytes observed in cases of essential purpura were almost all young, owing, the authors believe, to inhibition of normal maturation The platelets, they found, were reduced equally in the bone marrow and in the peripheral blood According to these investigators, the beneficial effect of splenectomy lies in the elimination of the inhibitory action on the development of megakaryocytes, thus enabling the bone marrow to revert to normal conditions Observations somewhat at variance with those of Limaizi and Schleicher but leading to essentially the same conclusions are reported by Revol²¹¹ Examinations of the material obtained by a series of sternal marrow aspirations performed before and after splenectomy on a patient suffering with thrombopenic purpura indicated a failure of release of platelets by the megakaryocytes Morphologically these giant cells appeared to be mature and identical with those present in normal marrow, but, until the spleen was removed, they failed to break up into thrombocytes The author postulates an inhibitory action of the spleen on platelet release Greiner²¹² reports a case of essential purpura in which the platelet count was low during hemorrhagic episodes, but the number could not be correlated with the bleeding time A correlation was, however, established between the level of the platelets and the degree of clot retraction After severe hemorrhages morphologic changes in the thrombocytes were noted, with the appearance of large, irregular and deeply stained forms In this case tests showed that capillary resistance was normal No treatment offered more than transient benefit Splenectomy was performed, with subsequent cessation of bleeding, but after nine and one-half months relapse occurred

The onset of thrombopenic purpura at puberty or shortly thereafter has been noted by many observers Two such occurrences are reported by Goldburgh and Gouley,²¹³ who mention other instances described

210 Limaizi, L. R., and Schleicher, E. M. The Reaction of Peripheral Blood and Bone Marrow in Chronic Hemorrhage and in Essential Thrombopenic Purpura, *J. A. M. A.* **114** 12 (Jan. 6) 1940

211 Revol, L. Etude du myelogramme dans un cas de purpura hémorragique avec thrombopénie, modifications à la suite de la splenectomie, *Sang* **13** 884, 1939

212 Greiner, K. Zur Klinik und Therapie der essentiellen Thrombopenie, *Ann. pædiat.* **154** 265, 1940

213 Goldburgh, H. L., and Gouley, B. A. Postpubertal Menorrhagia and Its Possible Relations to Thrombocytopenic Purpura Haemorrhagica, *Am. J. M. Sc.* **200** 499, 1940

in the literature According to these authors, evidences of abnormal coagulation develop gradually, and excessive loss of menstrual blood may precede by many months detectable platelet deficiency, prolonged bleeding time, increased capillary permeability and spontaneous purpuric manifestations It is suggested that abnormalities of the menstrual cycle, perhaps concerned with the corpus luteum, may lead to stimulation of the thrombocytolytic activity of the spleen Snaith²¹⁴ reports the case of a married woman of 27 in whom menorrhagia was the only hemorrhagic symptom associated with thrombopenia Recovery followed splenectomy

An interesting observation on the control of bleeding in patients afflicted with thrombopenic purpura is described by Tzanck, Sureau and Dreyfuss²¹⁵ They found transfusions of fresh blood and intravenous injections of platelet extracts valueless for this purpose However, in 3 cases hemorrhage ceased after the administration of blood which had been stored for ten days The phenomenon was ascribed to a combination of circumstances, including the presence in the blood of products of platelet disintegration and active ferments, lowering of the alkalinity of the plasma and increase in lactic acid content After fifteen days of storage the blood no longer possessed ferment activity and was ineffective in the control of bleeding

Intracranial hemorrhage occurs not infrequently in the course of thrombopenic purpura and is responsible for the death of many patients with this disorder However, as the first evidence of hemorrhagic proclivity it is exceedingly rare A case is reported by Gitt and Weiss²¹⁶ A youth aged 18 suffered an abrupt onset of symptoms associated with bloody spinal fluid, retinal hemorrhages and hematemesis An apparent cure followed removal of the spleen

Further evidence of the possible beneficial effects of solution of parathyroid administered to patients suffering with thrombopenic purpura is announced by Levine and Michelson²¹⁷ A 12 year old girl was given a total of 400 units of solution of parathyroid after splenectomy had failed to induce remission Symptomatic improvement ensued, but the platelet level remained low, and two months after removal of the

214 Snaith, L Menorrhagia Due to Essential Thrombocytopenia, *Lancet* **2** 684, 1940

215 Tzanck, A, Sureau, M, and Dreyfuss, A Trois cas de thrombopenie aigue Arrêt des hemorrhagies par transfusion de sang conserve âge de 10 jours, *Sang* **13** 996, 1939

216 Gitt, J J, and Weiss, E J Subarachnoid Hemorrhage as a Primary Manifestation of Thrombocytopenic Purpura, Splenectomy and Recovery, *J Missouri M A* **37** 73, 1940

217 Levine, D B, and Michelson, H Acute Thrombopenic Purpura Treated Successfully with Solution of Parathyroid, *J A M A* **115** 360 (Aug 3) 1940

spleen the thrombocytes numbered 75,000 per cubic millimeter. Aspiration of sternal marrow two weeks after splenectomy revealed little evidence of megakaryocyte maturation. Remission continued during an eleven month period of observation.

According to Priestley,²¹⁸ a woman aged 20 underwent splenectomy for thrombopenic purpura, and during convalescence typical infectious mononucleosis developed.

The case of a 2 month old boy with an extensive benign capillary hemangioma and associated thrombopenic purpura is reported by Kasabach and Merritt.²¹⁹ The hemangioma responded to roentgen therapy, and the purpura disappeared spontaneously.

Interest continues in the effect of splenic extracts on the platelet level of rabbit blood. Hodge and Strong²²⁰ prepared acetone extracts of the spleens of 2 patients suffering with thrombopenic purpura and observed no effects on the numbers of erythrocytes and platelets or the bleeding and clotting times of the blood of rabbits to which the material was administered. On the other hand, one of the few qualifiedly favorable reports on the platelet-reducing action of such extracts has been published by Hobson and Witts.²²¹ When relatively large doses were used it was found that the acetone extract of spleen obtained from a patient suffering with essential purpura was more effective than an extract prepared from the spleen of a healthy person in reducing the number of platelets in rabbit's blood. These authors also observed that an emulsion of normal spleen in Ringer's solution was more active than an acetone extract of the same material in bringing about decrease of thrombocytes in rabbits.

Secondary Thrombopenic Purpura. Among the toxic effects of the arsphenamines and related compounds on the blood-forming organs, thrombopenic purpura is of especial interest because of its sudden onset, its usually short duration, its association with increased capillary permeability and the lack of evidence of involvement of marrow elements other than platelets. This condition is to be distinguished from the general and prolonged myeloid hypoplasia, including involvement of the platelet-forming elements, which may also follow administration of arsphenamine. A number of reports of clinical and experimental inves-

218 Priestley, J. H. Thrombocytopenic Purpura Treated by Splenectomy and Complicated by Infectious Mononucleosis, *M. J. Australia* **1** 898, 1940.

219 Kasabach, H. H., and Merritt, K. K. Capillary Hemangioma with Extensive Purpura. Report of a Case, *Am. J. Dis. Child* **59** 1063 (May) 1940.

220 Hodge, I. G., and Strong, P. T. The Effect of Splenic Extracts of Patients with Thrombocytopenic Purpura on the Platelet Count of Rabbits, *Bull. Ayer Clin. Lab., Pennsylvania Hosp.* **3** 267, 1939.

221 Hobson, F. C. G., and Witts, L. J. Platelet-Reducing Extracts of the Spleen, *Brit. M. J.* **1** 50, 1940.

tigation have indicated that low ascorbic acid content of the blood and tissues may be associated with increased susceptibility to the toxic effects of the arsenicals used in the treatment of syphilis, but there has been no unanimity of opinion on the subject. The literature dealing with this question has been reviewed by Falconer, Epstein and Mills²²². They report clinical studies made on 6 patients known to be sensitive to neoarsphenamine and 1 sensitive to bismarsen. It was not possible to standardize the sensitivity reactions of these patients in terms of the size of the dose of the drug to which they were sensitive, but no appreciable modifications of sensitivity reactions were observed either during or after administration of ascorbic acid. The authors noted, in agreement with others, that the fall in the number of platelets does not closely parallel the severity of the purpuric manifestations associated with sensitivity reactions and, therefore, concluded that a capillary defect is largely responsible for the bleeding tendency.

A case is reported by Gorrie²²³ of thrombopenic purpura following seven injections of neoarsphenamine which was successfully treated with vitamin P. However, the blood picture indicated that in this case the patient was suffering from generalized myeloid hypoplasia, and the favorable result may be attributed to the self-limited course of the process.

Forty-two cases of thrombopenic purpura following ingestion of sedormid (allylisopropylacetylcarbamide) have been compiled from the literature by Falconer and Schumacher²²⁴. In the 36 cases in which the sex was reported, 24 of the patients were females and 12 were males. There appeared to be increased susceptibility among older persons. The authors report an additional case, with observations of the marrow. Granulocytic elements were increased, whereas erythropoiesis appeared to be reduced, although the change may have been merely relative. The number of megakaryocytes seemed to be unaffected. Administration of vitamin C was without therapeutic effect.

A case of thrombopenic purpura developing during the course of gold therapy is described by Invaldi and Gaspary²²⁵. Many megakaryocytes were observed in the sternal marrow of their patient, who subsequently recovered.

222 Falconer, E. H., Epstein, N. N., and Mills, E. S. Purpura Haemorrhagica Due to Arsphenamine. Sensitivity in Patients as Influenced by Vitamin C Therapy, *Arch Int Med* **66** 319 (Aug) 1940.

223 Gorrie, D. R. Purpura Haemorrhagica After Arsenic Therapy Treated with Vitamin P, *Lancet* **1** 1005, 1940.

224 Falconer, E. H., and Schumacher, I. C. Purpura Haemorrhagica Due to Ingestion of Sedormid (Allylisopropylacetylcarbamide). Experimental Observations and Report of Case, *Arch Int Med* **65** 122 (Jan) 1940.

225 Invaldi, A., and Gaspary, F. Purpura hemorragica en el curso de la crisoterapia, *Rev med de Rosario* **30** 475, 1940.

Two cases of thrombopenic purpura due to sulfapyridine are reported by Russell and Page²²⁶. In 1 death occurred. Examination of the marrow revealed slight increase in megakaryocytes and active erythropoiesis.

A case reported by Regamey²²⁷ is of especial interest because the provocative agent, the type of onset and the associated symptoms are more characteristic of Henoch's purpura than of thrombopenic purpura. A 28 year old woman was vaccinated, with a marked "take," and five weeks later suffered an abrupt attack of severe abdominal pain, followed by epistaxis, hematemesis, melena and metrorrhagia. Examination revealed generalized petechiae, ecchymoses and hemorrhagic pustules. The platelet count was 30,000 per cubic millimeter, and the sternal marrow contained many immature megakaryocytes. Recovery was rapid, and one month after the hemorrhagic episode the blood and marrow were entirely normal.

Alt, Carroll and Doherty²²⁸ report the case of a young primipara in the sixth month of gestation who was admitted to the hospital because of acute catarrhal jaundice. On admission the number of platelets was approximately 175,000 per cubic millimeter, and in other respects the blood was normal, except for leukopenia. Soon thereafter the platelets disappeared completely from the blood, and severe hemorrhagic manifestations occurred. Capillary resistance was decreased. After three weeks of serious illness, the jaundice and purpura disappeared and the patient went on to uneventful delivery.

Nonthrombopenic Purpura. All patients exhibiting a hemorrhagic tendency should have the benefit of a capillary resistance test, according to Madison and Squier²²⁹. Impaired capillary integrity has been associated, in their experience, with vitamin C deficiency, severe infections, the terminal phase of neoplastic disease, malignant hypertension, primary blood dyscrasias, allergic states and ovarian disorders.

Children manifesting vascular purpura due to various causes were treated with a vitamin P concentrate by Kugelmass²³⁰. Cases of nutritional deficiency, allergy, infection and trauma were represented. The medication employed was 150 mg. of a solution of eriodictyol glucoside

226 Russell, H. K., and Page, R. C. Thrombocytopenic Purpura Due to Sulfapyridine, *Am J M Sc* **200** 495, 1940.

227 Regamey, E. Crise aigue de purpura thrombopenique consécutive à une generalisation vaccinale tardive, *Schweiz med Wchnschr* **70** 697, 1940.

228 Alt, H. L., Carroll, H. B., and Doherty, C. C. Thrombopenic Purpura Associated with Catarrhal Jaundice. Report of a Case During Pregnancy, *Quart Bull Northwestern Univ M School* **14** 183, 1940.

229 Madison, F. W., and Squier, T. S. Bleeding Due to Capillary Defect, *Wisconsin M J* **39** 31, 1940.

230 Kugelmass, I. N. Vitamin P in Vascular Purpura, *J A M A* **115** 519 (Aug 17) 1940.

and hesperidin, administered orally each day. Successful results were obtained in all cases except those of traumatic or mechanical vascular purpura.

A case of Henoch's purpura complicated by intussusception, occurring in a boy of 3 years, is reported by Schwartzman²³¹. A number of similar instances are to be found in the literature before 1940.

Reid²³² reports the case of a 71 year old woman who had suffered with prolonged bleeding and recurring hematomas for many years. The platelets numbered more than 1,000,000 per cubic millimeter, and megakaryocytes were unusually numerous in the bone marrow. According to the author, 5 similar cases have been recorded in the literature. Characteristics of the disorder include prolonged bleeding time, normal coagulation time, platelets often in excess of 1,500,000 per cubic millimeter and leukocytosis, with a white cell count ranging from 12,000 to 43,000 per cubic millimeter. There are neutrophilia, occasionally monocytois and sometimes eosinophilia. Examination of the blood revealed myelocytes in 3 cases and myeloblasts in 1. The spleen was enlarged in 4 cases, and examination of the bone marrow in 3 revealed increased erythropoiesis and granulopoiesis and excessive numbers of megakaryocytes and platelets.

Hereditary conditions characterized by a tendency to bleed are classified by Bruun²³³ as hemophilia, essential thrombopenia (Weillhof) and hereditary thrombasthenia, or pseudohemophilia (Glanzmann). To this list he adds a condition observed among 23 members of a single family, including four generations. Of these, 15 exhibited a definite bleeding tendency and 3 others had some evidence of a hemorrhagic disorder. Common to all the subjects were normal coagulation and bleeding times and normal number of platelets. Although this condition may be identical with that described by Glanzmann as hereditary thrombasthenia the author obtained no evidence of pathologic platelet behavior. He prefers the term hereditary hemorrhagic diathesis to a more specific designation.

Hemophilia. Few contributions to the literature on hemophilia appeared during 1940. Dam and Venndt²³⁴ report experiments on heparinized plasma of hemophilic and of normal persons designed to determine the coagulating effects on such plasma of tissue extracts and platelet suspensions. The results indicated that the coagulation defect in hemophilia consisted of reduced ability of the plasma to clot in the

231 Schwartzman, J. Henoch's Purpura with Intussusception, *Arch. Pediat.* **57** 389, 1940.

232 Reid, J. Haemorrhagic Thrombocythaemia, *Lancet* **2** 584, 1940.

233 Bruun, E. Hereditary Hemorrhagic Diathesis, *Acta med. Scandinav.* **102** 639, 1939.

234 Dam, H., and Venndt, H. Observations on the Coagulation of Blood Plasma in Hemophilia, *Lancet* **1** 70, 1940.

presence of small quantities of tissue extract, such as might be liberated from mechanically damaged cells, whereas no difference in the clotting behavior of hemophilic and of normal plasma was found when large quantities of tissue extract were employed. The use of platelet suspensions revealed a greater difference in the clotting responses of the two types of plasma than was observed when tissue extracts were added.

A review of hemophilic arthropathies, together with the presentation of 5 cases, with roentgenograms, is published by Caffey and Schlesinger²³⁵. The authors describe the characteristic features produced by intra-articular, intraosseous and subperiosteal hemorrhages. Dysgenesis was present in the capitulum of the radius in 2 cases and in the proximal epiphysis of the femur in 1 case.

Oxalic acid was given intravenously in doses of 3 to 12 mg daily to 3 hemophilic patients by Page, Russell and Rosenthal²³⁶. They report that within two or three days after this treatment was begun the coagulation time became normal. When the drug was discontinued the clotting time returned to its previous value. No evidences of toxicity of the drug were observed. The authors suggest that oxalic acid may alter the surface tension of the platelet membrane in such a way that disintegration occurs more readily. The treatment may be of value in controlling hemorrhagic episodes of hemophilic patients.

A note on the progress of 3 patients suffering with hemophilia is given by Lawson and Graybeal²³⁷. In a previous article concerning these patients the authors reported on treatment by venesection. Since the last report 2 of the patients have died as the result of hemorrhage.

A competent review of the recent literature on hemophilia, with a discussion of therapeutic agents used in this disease, has been published by McGavack²³⁸.

AGRANULOCYTOSIS

A perusal of the literature for the past year has not revealed any new information dealing with agranulocytosis which will lead to an important revision of our ideas concerning the cause, diagnosis or treatment of the disease. It is of interest, however, that the history

235 Caffey, J., and Schlesinger, E. R. Certain Effects of Hemophilia on the Growing Skeleton. Some Roentgenographic Observations on Overgrowth and Dysgeneses of Epiphyses Associated with Chronic Hemarthrosis, *J. Pediat.* **16** 549, 1940.

236 Page, R. C., Russell, H. K., and Rosenthal, R. L. Effect of Oxalic Acid Intravenously on Blood-Coagulation Time in Three Hemophiliacs, *Ann. Int. Med.* **14** 78, 1940.

237 Lawson, G. B., and Graybeal, A. B. Hemophilia Treated by Venesection. *J. A. M. A.* **114** 2299 (June 8) 1940.

238 McGavack, T. H. Some Recent Advances in the Treatment of Hemophilia, *M. Clin. North America* **24** 791, 1940.

of 1 case is presented in which the condition was apparently due to alurate (allylisopropylbarbituric acid). This is the most convincing evidence that a barbiturate can be responsible for the syndrome. In 1 instance it was suggested that acetophenetidin was the responsible etiologic agent, but the evidence was purely circumstantial. Cases continue to be recorded in which the disease was due to aminopyrine, prescribed in such proprietary preparations as pyramidon and causalin. A number of cases in which the condition was attributed to sulfanilamide or to sulfapyridine were reported last year. It had been rather generally assumed that the condition did not arise from sulfapyridine until 50 Gm or more had been given, but the literature for the year contains data which appear to refute this belief. An increasing number of cases have occurred in which the condition was due to gold therapy, which is understandable on account of the greater use of gold salts in the treatment of arthritis.

Drevermann and Gardner²³⁹ state that, although in a majority of the cases agranulocytosis can be attributed with a high degree of probability to known causal agents, there still remains a small proportion in which the disease must be regarded as idiopathic. Although the condition may occur as the result of any one of many drugs, the etiologic relationship is clearly defined only in the case of aminopyrine and its derivatives. This is because it is only for the leukopenia due to this drug that the criteria of Kracke have been fulfilled, namely: 1. It is necessary for the drug to produce leukopenia in a patient who has recovered. 2. Other leukocytic depressants must be eliminated. 3. The leukopenia must be differentiated from that of sepsis or of other blood dyscrasias. An excellent review is given of knowledge regarding the symptoms and signs, the differential diagnosis, the pathologic lesions and treatment of the syndrome. The authors recommend, as the best form of therapy, pentnucleotide and yellow bone marrow given simultaneously. It is their opinion that each plays a part in the maturation of the polymorphonuclear cell. In some cases, they believe liver extract may be beneficial. Six patients with agranulocytosis were treated with yellow bone marrow and pentnucleotide, and the response was such that the authors believe the preparations to be effective. The same type of treatment was tried for patients with myelogenous leukemia, lymphatic leukemia, monocytic leukemia and aplastic anemia, but it was ineffective.

Strumia,²⁴⁰ in a general article on the changes in the leukocytes in which leukopenia is discussed, states that physiologic leukopenia is

239 Drevermann, E. B., and Gardner, H. J. Schultz Syndrome (Granulocytopenia), with Special Reference to Its Treatment with Extract of Yellow Bone Marrow, *M. J. Australia* **1**: 851, 1940.

240 Strumia, M. M. Clinical Interpretation of Leukocytic Pictures, *Pennsylvania M. J.* **43**: 1556, 1940.

are Occasionally a person otherwise in perfect health will have a white blood cell count between 4,000 and 5,000 per cubic millimeter. Counts below 4,000 per cubic millimeter must be considered as abnormal. The most common causes of leukopenia are infection, such poisons as benzene compounds, exposure to roentgen rays or to radium, disease of the bone marrow (aplastic anemia, agranulocytosis, pernicious anemia and myelophthisic disease), anaphylactic shock and malnutrition. He emphasizes that the most severe form of leukopenia occurs in agranulocytosis.

Pewny²⁴¹ has attempted to establish a syndrome which he has termed agranulocytosis forme fruste, but the clinical and hematologic features described do not convince one that such a clinical entity exists. The condition, he claims, is characterized by epistaxis and a tendency to bleed which may prove "mortal" if a surgical operation is performed when a patient is in this state. The syndrome is said to be characterized also by leukopenia, with a reduction in the number of granular cells of the circulating blood, the polymorphonuclear cells show a definite shift to the left, even to the development of a "myeloid reaction." The author states that such patients have transient and mild damage to the bone marrow as evidenced by a delay in the maturation process of the granulocytes and the megakaryocytes. Treatment recommended is symptomatic, with the administration of almost all drugs which have been employed in the treatment of true agranulocytosis.

Lin and Isaacs²⁴² found that a single injection of the water-soluble potassium salt of dicarboxybenzantracene into Swiss mice is followed by a striking decrease in the number of polymorphonuclear neutrophils. The absolute number of these cells fell from an average of 5,448 to one of 1,299 per cubic millimeter during the third week after an injection. There was a slower and more moderate decrease in the number of monocytes, with but slight change in the number of lymphocytes, eosinophils and basophils. Recovery is complete seven weeks after the last injection. Further studies may lead to the development of a method whereby experimental agranulocytosis may be produced in animals.

Day and associates²⁴³ report that when young rhesus monkeys were given a diet essentially the same as the Goldberger black tongue-producing diet, leukopenia, with a white cell count as low as 700 cells per cubic millimeter, anemia, gingivitis and diarrhea developed and

241 Pewny, W. Agranulocytosis Forme Fruste, *New York State J. Med.* **40** 1236, 1940.

242 Lin, H. A. C., and Isaacs, R. Production of Neutropenia in Swiss Mice by Injection of Potassium Dicarboxy-Benzanthracene, *Proc. Soc. Exper. Biol. & Med.* **43** 551, 1940.

243 Day, P. L., Langston, W. C., Darby, W. J., Wahlin, J. G., and Mims, V. Nutritional Cytopenia in Monkeys Receiving Goldberger Diet, *J. Exper. Med.* **72** 463, 1940.

the animals died. Supplementing this diet with ascorbic acid, thiamine hydrochloride, nicotinic acid and riboflavin failed to prevent the appearance of the syndrome. The addition of the combination of ascorbic acid and liver extract was effective, as was a supplement of a crude liver extract. The ash of liver extract, however, failed to maintain a normal blood picture or to prolong life. The authors concluded that the diet was deficient in a substance which they had previously termed vitamin M and that this deficiency was responsible for the pathologic changes. While these experimental results may not have a bearing on acute agranulocytosis, they may offer an explanation for some of the chronic types of granulocytopenia of which the etiologic relations are unknown.

A case of granulocytopenia following barbiturate therapy, reported by Hadler,²⁴⁴ is of extreme interest and importance because convincing evidence is presented that agranulocytosis did develop following test doses of alurate. The patient, a married woman aged 30, had previously been healthy, except for several attacks of asthmatic bronchitis. She was first admitted to the hospital on account of an infection of the upper respiratory tract and bronchitis. At this time, it was observed that the administration of allonal was followed by a shaking chill and a period of malaise. Before January 1939 allonal consisted of alurate and aminopyrine, but since then each dose has been composed of 1 grain (0.06 Gm.) of alurate and 3 grains (0.19 Gm.) of acetophenetidin. It was suspected that the patient was sensitive to alurate and as a test $\frac{1}{3}$ capsule (0.07 Gm.) of sodium alurate was given on the evenings of August 1 and 2. On August 3 the total white cell count was 2,800 per cubic millimeter and the percentage of polymorphonuclears 63. The number of polymorphonuclear leukocytes remained low, on August 8 the total white cell count was 1,800 per cubic millimeter and no polymorphonuclear cells were present. After she ingested the drug, the patient's body temperature rose to 102 F., and she had chills and sweats. The gums became sore, and two spots of exudate appeared in the right tonsillar region. The patient made a complete recovery after the use of reticulogen (a concentrated liver extract) and pentnucleotide. Although this article is based on a single case history, it is one of great importance, for it brings up again for discussion the possibility that barbiturates may be responsible for the production of agranulocytosis. A great deal has been said about this in the past, and practically all observers had reached the conclusion that this type of drug was not responsible for the syndrome. Now, this case report is presented which appears to offer convincing evidence that this particular type of barbiturate may be a causative agent. Certainly, proved cases are rare. The author

244 Hadler, A. J. Granulocytopenia Following Barbiturate Therapy. Report of Case, *New England J. Med.* **222**: 755, 1940.

points out that alurate (allylisopropylbarbituric acid) and sedormid (allylisopropylacetaylcarbamide) are similar in structure. The latter drug, in recent years, has been known to produce thrombopenic purpura, and occasionally its use has been followed by a rather marked leukopenia, although it has not caused true agranulocytosis.

Kopp²⁴⁵ reports the case of a patient who had a chronic and symptomatic leukopenia of four and one-half years' duration, which terminated fatally in typical agranulocytic angina. On each examination of the blood during 1934 and 1938 the patient presented a decided reduction in the number of leukocytes, with counts as low as 1,000 per cubic millimeter. The various white cell elements were quantitatively but not qualitatively affected. No cause could be found for the leukopenia, and although the reduction of white cells was at times striking, the patient enjoyed good health for four and one-half years. No examinations of the blood were made between 1934 and 1938, so it is not known whether the leukopenia was present in the interim. Until the onset of the acute disease the patient had taken only potassium iodide, acetylsalicylic acid and sodium amytal. Just prior to the development of the fatal agranulocytosis he was given fairly large doses of preparations containing acetophenetidin. On the patient's admission to the hospital, the white cell count was found to be 350 per cubic millimeter and only a few granular cells were noted on the blood film. Treatment was with a transfusion and adenosine sulfate. Kopp believes that this case strongly supports the theory that agranulocytic angina tends to occur in persons in whom a bone marrow dyscrasia is already present, with a resultant diminution of the granular cells in the peripheral blood stream.

The case of a white woman aged 41 in whom agranulocytosis developed after the use of capsules containing aminopyrine and codeine sulfate for the relief of uterine symptoms is reported by Bailey and Katzen²⁴⁶. Later ulcerative lesions of the mouth developed, for which therapy with azosulfamide (disodium 4-sulfamidophenyl-2'-azo-7'-acetylamino-1'-hydroxynaphthalene 3',6'-disulfonate) was instituted. It appeared to the authors that this substance "caused further destruction of the granulocytes." Twelve hours before death examination of the blood yielded the following information: red cell count 3,400,000 per cubic millimeter, percentage of hemoglobin 70 and white cell count 200 per cubic millimeter. Examination of a blood film showed complete absence of neutrophils. The patient died twelve hours after

245 Kopp, I. Chronic Leukopenia with Fatal Termination Due to Agranulocytic Angina. Case Report, *Ann Int Med* **13** 2347, 1940.

246 Bailey, J. H., and Katzen, B. Case of Agranulocytosis Following Use of Pyramidon and Neoprontosil, *Virginia M. Monthly* **67** 112, 1940.

treatment was instituted with an oxygen tent, administration of pentnucleotide and blood transfusion

Berghausen²⁴⁷ states that when aminopyrine is prescribed the physician should be on the alert for possible toxic symptoms. Unfortunately, it is not always recognized that a drug bearing a trade name contains aminopyrine. Such a drug is *causalin*, each 7.5 grain (0.5 Gm.) tablet of which was stated by Berghausen, citing Bernhard, to contain 1.82 grains (0.12 Gm.) of aminopyrine. He reports the case of a 52 year old woman who had been taking such a tablet three times daily for a month, on the advice of her physician, for the relief of arthritis. An acute illness developed. On admission to the hospital the patient was exceedingly toxic, the temperature was 102 F., there was ulceration on the hard palate and the pharynx was swollen and edematous. The white blood cells numbered 1,150 per cubic millimeter, and there were no granular cells present in the stained blood film. Sternal puncture showed that all of the white cells were lymphocytes, the red blood cells were normal in size and normoblasts were absent. The patient died on the day following admission. The only therapy was a 10 per cent solution of dextrose given intravenously.

It is pointed out by Mirick²⁴⁸ that since the introduction of sodium gold thiosulfate by Mollgaard, of Copenhagen, Denmark, in 1924, the popularity of gold salts as therapeutic agents has steadily increased in treatment of tuberculosis, chronic rheumatism, lupus erythematosus and various other diseases. The reluctance to utilize gold salts in this country has been due to the fear of toxic reactions, which have been carefully reported and analyzed by Hartfall, Garland and Goldie.²⁴⁹ Mirick has reviewed the cases reported in the literature, collected 17 other cases and added one of his own, in which there was complete agranulocytosis with recovery. The patient was a woman aged 22 who had suffered from rheumatoid arthritis and questionable pulmonary tuberculosis for one year. She received a total dose of 0.825 Gm. of sodium gold thiosulfate, chiefly intramuscularly, over an interval of twenty-one days. The first indication of a hematologic complication appeared at the end of that time, when it was noted that the total leukocyte count was 3,880 per cubic millimeter and the percentage of polymorphonuclear cells and basophils was 22. The diminution in the number of granulocytes became progressively greater, until twelve days later they completely disappeared from the blood stream. There was

247 Berghausen, O. Fatal Leukopenia Following Internal Administration of *Causalin*, *J. A. M. A.* **114** 1547 (April 20) 1940.

248 Mirick, G. S. Total Agranulocytosis Following Gold Therapy. Report of Case with Recovery and Review of Literature, *Am. Rev. Tuberc.* **41** 344, 1940.

249 Hartfall, A. J., Garland, H. G., and Goldie, W. Gold Treatment of Arthritis. Review of Nine Hundred Cases, *Lancet* **2** 784 and 838, 1937.

no significant change in the red blood cells at any time. The only other untoward symptom associated with gold therapy was a mild and transient cutaneous rash, which appeared a few days after the granulocytopenia became apparent. After complete agranulocytosis had been present for three days, the polymorphonuclear cells reappeared, and their percentage and the total leukocyte count returned to normal. This recovery followed the administration of liver extract, blood transfusions, pentnucleotide and ferrous sulfate. The only other drug used was sodium amytal, which was employed for sedation. There was no history of the ingestion of other drugs which might have been responsible for the agranulocytosis. Despite the unpleasant and serious complication following the gold therapy, the patient experienced striking improvement in her rheumatic complaints and left the hospital feeling better than she had at any time since the onset of her illness.

An excellent and comprehensive summary of the previously reported cases in which agranulocytosis developed after gold therapy is given by Mirick. In 18 such case reports studied, there were 9 instances of "rheumatism" and 9 of tuberculosis, 14 patients were female and 4 were male and 9 patients died and 9 recovered. The interval between the first injection of gold salts and the onset of the agranulocytosis varied from twelve to about one hundred and eighty days, in 9 cases the interval was thirty days or less. Five different gold preparations were given, as follows: crisalbine (sodium gold thiosulfate), sanocrysin (sodium gold thiosulfate), allochrysin (sodium aurothiopropionol sulfonate), solganol B (aurothiodextrose) and lopion (sodium auroallylthiourea benzoate).

There is no evidence that incriminates any one preparation, nor does the dosage appear to play a role in either the causation of the complication or the prognosis. The latter conclusion is supported by the fact that the patients who died received between 0.8 and 3.5 Gm. of the salt, with an average of 1.29 Gm., whereas the patients who recovered received from 0.08 to 4.5 Gm., with an average of 1.26 Gm. On the other hand, the author claims that there is some prognostic information of value to be derived from the absolute number of polymorphonuclear cells and basophils present in the circulating blood. He notes that in those cases in which the absolute number was below 34 the mortality was 75 per cent, whereas if the lowest number was 36 or more, recovery followed in all cases. He also states that the presence of eosinophilia is a good prognostic sign. It is concluded that the evidence incriminating gold salts as a cause of agranulocytosis is circumstantial and therefore presumptive. Agranulocytosis has occurred in the past, not infrequently, in patients with "chronic rheumatism" because they have been prone to employ aminopyrine therapeutically. This cannot be said, how-

ever, to apply necessarily to patients with tuberculosis. The only conclusive evidence that the disease can be due to gold salts must be obtained by producing the condition experimentally in animals or in patients who have previously experienced an attack. A warning is given not to administer gold salts to patients who have hepatic disease, hemorrhagic states, allergic conditions or eczema. There is no evidence that cutaneous tests with gold preparations will enable one to avert untoward complications. The author concludes that agranulocytosis supervenes in about 1 case in 1,000 in which gold salts are given, in about one half of the cases in which this condition develops the patients recover, and in an equal number they succumb, neither age, sex, underlying disease, dosage of the gold salts, the preparation employed nor length of time between the onset of therapy and appearance of the agranulocytosis seemed to make any difference in the prognosis. In his opinion, the relationship between the gold salts and the blood changes remains unsettled, but the cases reported support the concept that gold may be the cause of agranulocytosis in some cases. The article is one of singular value on account of the adequately detailed case report and the admirable review of the literature.

Anderson and Palmer²⁵⁰ state that gold salts are being used with increasing frequency in the treatment of arthritis, lupus erythematosus, cutaneous tuberculides and syphilis. Among the hematologic complications which may develop after such therapy are purpura, granulocytopenia, hypochromic anemia and aplastic anemia. This article is a complete summary of all the untoward complications which may follow the administration of gold preparations.

Sweeney and Allday²⁵¹ reemphasize that physicians who give sulfanilamide to patients should be on the alert for the development of agranulocytosis, which will appear in the occasional person who is susceptible to the drug. They report the case of a woman aged 41 who received 20 Gm of sulfanilamide over a period of eight days for acute pharyngitis. At the end of this time the white cell count was 1,800 per cubic millimeter, with 4 per cent polymorphonuclear cells, the red cell count was 2,680,000 per cubic millimeter and the hemoglobin concentration was 42 per cent. Treatment consisted of daily transfusions of 300 cc of blood for seven days. At this time there was a "remarkable" crisis, characterized by a critical drop in the body temperature to subnormal, a striking increase in the polymorphonuclear cells and evidence of general improvement in the patient. The crisis described resembles

250 Anderson, N. L., and Palmer, W. L. The Danger of Gold Salt Therapy. Report of Fatal Case, *J. A. M. A.* **115** 1627 (Nov. 9) 1940.

251 Sweeney, J. S., and Allday, L. E. Granulocytopenia from Sulfanilamide with Unusual Blood Crisis and Recovery. Case Report, *Ann. Int. Med.* **13** 1241, 1940.

that seen in pneumonia. We also have observed similar and dramatic improvement in patients with agranulocytosis, although previous mention of this has not been observed in the literature.

A case of agranulocytosis is reported by Robb²⁵² in which ingestion of 36 Gm of sulfanilamide over a period of three weeks was followed by death. This medicament was obtained by the patient from a drug-store, apparently without a prescription, for the treatment of a urethral discharge. He was admitted to the hospital with a high fever and the following day complained of sore throat. On admission he had 2,400 white blood cells per cubic millimeter, with no granulocytes present in the blood film, the hemoglobin concentration was 59 per cent, and the red blood cell count, 3,520,000 per cubic millimeter. He died on the fifth day in the hospital, despite the use of 120 cc of pentnucleotide for four days, the injection of liver extract daily and three blood transfusions. The clinical diagnosis was acute agranulocytosis due to sulfanilamide, with terminal bronchopneumonia. At necropsy, the striking feature of the bone marrow was the presence of few granular cells.

Anderson, Horowitz and Palmer²⁵³ report the case of a 32 year old woman with a mild "simple" anemia, an inflamed throat and an infection of the urinary tract, in whom pleuropneumonia developed. Treatment was with sulfapyridine, and she received 75 Gm in divided doses over a month. The blood at the end of this time showed 38 per cent hemoglobin and 1,210,000 red cells and 1,940 white cell per cubic millimeter. The following day the white cell count was 3,800 per cubic millimeter, with 24 per cent granulocytes. Sternal puncture showed an enormous increase in myelocytes and myeloblasts in the marrow and almost complete absence of older forms of these cells. Treatment was with pent nucleotide in an 8 per cent solution, 10 cc being given intramuscularly in four doses in the three days preceding death. Also, liver extract was administered, without avail. The patient was considered to have a "maturation type" of agranulocytosis occurring after the use of sulfapyridine. The results of necropsy were consistent with this diagnosis.

Tragerman and Goto¹⁰¹ warn against the use of sulfanilamide and its derivatives without adequate supervision, as fatal complications due to granulocytopenia, hemolytic anemia and damaged liver may occur. Three of the 5 deaths following sulfanilamide or sulfapyridine therapy encountered in the autopsy service of the Los Angeles County Hospital

252 Robb, J. P. Fatal Case of Agranulocytosis Following Use of Sulfanilamide, *Canad. M. A. J.* **42**: 268, 1940.

253 Anderson, W. K., Horowitz, S., and Palmer, T. W. Fatal Agranulocytosis After Sulfapyridine (M & B 693) Therapy, *Glasgow M. J.* **134**: 172, 1940.

were due to granulocytopenia. One patient was a boy aged 15 who received 100.6 Gm of sulfanilamide over a period of eighteen days. Three days after the drug had been discontinued, sore throat developed, with a body temperature of 104 F, reddened pharynx and injected ear drums. The white blood cell count was 675 per cubic millimeter, with no polymorphonuclear cells. The boy died on his second day in the hospital. Necropsy showed a reduction in the granulocyte series of cells, with arrest of maturation at the myelocyte level. A second patient was a 35 year old woman who took 64 Gm of sulfanilamide over a period of two weeks for a "streptococcic sore throat." Despite treatments with blood transfusions, pentnucleotide and liver extract she died on the third day of hospitalization. The bone marrow was not examined at necropsy. The third patient was a man aged 53 who had subacute bacterial endocarditis due to *Streptococcus viridans*, for which he was given 88.5 Gm of sulfapyridine over a twenty-one day period. At the end of this time the patient complained of sore throat, and examination of the blood showed 1,100 leukocytes per cubic millimeter, of which 22 per cent were polymorphonuclear cells. One blood transfusion was given, but the patient died six days after the sulfapyridine therapy was discontinued. At necropsy the bone marrow showed arrest of maturation at the myeloid level.

Sakula²⁵⁴ reports the case of a 2½ year old girl who recovered from meningitis caused by the Pfeiffer bacillus after the administration of sulfapyridine but in whom a granulocytopenia apparently due to the medication developed. The drug was given intermittently because of exacerbations and remissions of the disease and also because of the untoward reactions it produced. A total dose of 31 Gm was given over a period of twenty-four days. The first evidence of agranulocytosis appeared in the form of a leukocyte count of 3,000 per cubic millimeter, with 13 per cent polymorphonuclear cells. After the omission of the drug and the administration of pentnucleotide the child made an uneventful recovery. The author states that "numerous" cases of granulocytopenia, and even of agranulocytosis, have followed the use of the drug. He considers that danger of development of such a condition must be increased in children, for, in his opinion, their bone marrow is more susceptible to toxic damage. Frequent blood counts are recommended when the drug is given in large doses and for prolonged periods.

It has been commonly considered that development of agranulocytosis following sulfapyridine therapy is usually related to the amount of the drug given and to the duration of the treatment. The average dose followed by the development of agranulocytosis has been 50 Gm for

²⁵⁴ Sakula, J. Pfeiffer Bacillus Meningitis Successfully Treated with M and B 693, Complicated by Granulopenia, *Lancet* 1: 596, 1940.

an average period of twenty days Spain²⁵⁵ reports a case in which, he claims, the condition appeared after the administration of 4.5 Gm of sulfapyridine and 4.5 Gm of sulfanilamide over an interval of four days. The patient was a primipara aged 26 who was given the drugs on account of acute mastitis which developed ten days after a cesarean section. Three days after the medication was discontinued, the patient complained of a "sore throat" and the white blood cell count was found to be 1,920 per cubic millimeter, with 2 per cent granular cells. Despite treatment with pentnucleotide and blood transfusions, the patient died on the fifth day of her illness. Ordinarily, the presence of anemia casts doubt on the diagnosis of true agranulocytosis, as the leukopenia under such circumstances is often associated with some other type of blood dyscrasia, such as aplastic anemia or aleukemic leukemia. In this patient the hemoglobin concentration was 36 per cent and the red cell count 2,490,000 per cubic millimeter, which values could be accounted for by the drugs employed or by the presence of an iron-deficiency anemia of pregnancy and the loss of blood at the operation, which was reported as "moderately heavy." In other words, there is no reason why agranulocytosis might not develop in a patient with anemia.

Montuschi²⁵⁶ reports a case of agranulocytosis in a 15 month old infant after 17.5 Gm of sulfapyridine had been administered over a period of eight days. Twenty-four hours after the treatment had been initiated the sulfapyridine content of the spinal fluid was 8 mg per hundred cubic centimeters, and in fifty-two hours it was 4 mg per hundred cubic centimeters. After the temperature had decreased and other striking evidences of improvement appeared, the temperature again rose. This change led to an examination of the blood, and it was found that the total white cell count was 6,000 per cubic millimeter but that only 21 per cent of the cells were granulocytes. No ulcerative lesions of the mouth appeared at any time. The lowest absolute number of granulocytes during the course of the illness was 400 per cubic millimeter. Eosinophils reappeared in the blood on the fifth day of treatment with pentnucleotide, and this was promptly followed by the subsidence of all symptoms and complete recovery. The author is not entirely willing to credit the pentnucleotide with the cure, as he states that recovery may have been spontaneous. In such cases, however, he apparently considers its use advisable.

Leftwich²⁵⁷ reports the case of a native laborer who was admitted to the hospital with lobar pneumonia, for which he was given 42 Gm

255 Spain, A. W. Agranulocytosis Following Chemotherapy with Small Dosage, *Brit. M. J.* **1** 930, 1940.

256 Montuschi, E. Granulocytopenia Following Sulphapyridine Therapy, *Brit. M. J.* **1** 1055, 1940.

257 Leftwich, P. Agranulocytosis Complicating Treatment by Sulphapyridine (M. and B. 693), *South African M. J.* **14**:142, 1940.

of sulfapyridine over a period of twenty-one days. At the end of this time, because of the recurrence of fever, his blood was again examined and the total white cell count found to be 1,400 per cubic millimeter. No granulocytes were present, nor were any observed in the next three days before death. The author states that in most cases this syndrome develops after a total dose of 45 Gm. has been given, although he refers to 1 case in which only 18 Gm. of the drug had been taken in fifteen days. He warns that a rare case of agranulocytosis must be expected to appear, especially when the total dose is over 50 Gm. In any patient receiving the drug, the development of leukopenia should be suggested by a sudden aggravation of the toxemia, high fever, generalized aching or sore throat.

Erskine and Royds²⁵⁸ report the case of a man aged 29 in whom acute pemphigus developed nine days after he received a burn. As treatment a total of 35 Gm. of sulfapyridine was administered over a period of twenty-one days. At the end of this time the leukocyte count was 6,000 per cubic millimeter, with only 17 per cent of the cells of the polymorphonuclear type, 90 per cent of which were immature. There was also a fairly severe associated anemia, as the hemoglobin concentration was 52 per cent and the red cell count 2,860,000 per cubic millimeter. The case is reported as one of agranulocytosis due to the ingestion of 35 Gm. of sulfapyridine, with recovery following the discontinuance of the drug and the administration of liver extract and pentnucleotide.

Folkner, in "Conferences on Therapy,"²⁵⁹ expresses the belief that agranulocytosis is an acute episode with a definite syndrome which goes on either to death, in about 70 per cent of the cases, or to spontaneous, or possibly induced, recovery, in the remaining 30 per cent. His attitude is one of pessimism in regard to the effectiveness of any therapeutic agent which has been employed in this disease. This is indicated in the following statement:

As a matter of fact there has been no satisfactory study of a treated group of cases of agranulocytic angina and a control group comparable as to age, nutrition, general state of health and blood picture in which any therapeutic agent has been shown to be beneficial.

The most important factor in the treatment, he believes, is to remove the offending agent, if it can be found. Roentgen ray therapy he considers to be dangerous, there is no good evidence to support the view

²⁵⁸ Erskine, D., and Royds, J. E. Agranulocytosis Complicating Treatment of Acute Pemphigus with M & B 693, *Lancet* 2 1366, 1939.

²⁵⁹ Conferences on Therapy (From Cornell University Medical College and New York Hospital). Treatment of Blood Disorders, Leukemia, Agranulocytosis and Neutropenia, *J. A. M. A.* 115 126 (July 13) 1940.

that liver extract is helpful, pentnucleotide is not as effective as it was once thought to be, and observations do not indicate that blood transfusions are of value. We do not agree with Forkner in labeling as useless all forms of treatment which have been suggested for agranulocytosis. It is his opinion that evidence does exist which suggests strongly that pentnucleotide and blood transfusions are superior to other forms of therapy and should be employed in all cases.

INFECTIOUS MONONUCLEOSIS

During the past year probably the most important contribution to the literature dealing with infectious mononucleosis is the monograph by Bernstein. Other articles indicate and emphasize the importance of the diversity of the symptoms, the great diagnostic value of the heterophile antibody reaction and the presence of jaundice and anemia in some cases. The occurrence of the meningeal type of the disease, with a fatal termination in some instances, is discussed. Sulfanilamide and convalescent serum are the newest therapeutic agents which have been used. Bernstein's article²⁶⁰ of 64 pages, with 207 references, will be of inestimable assistance to all physicians who are interested in the condition. A digest of its contents is not possible in a review of this nature. It is highly recommended, however, to all those who desire to obtain an idea of the development and the present status of knowledge concerning the disease.

Kracke²⁶¹ considers that infectious mononucleosis is important because many new facts concerning the disease have been learned in recent years and because its manifestations are so protean. He states that the modern interest in the condition arose in 1920, when Spiunt and Evans applied the term "infectious mononucleosis." In 1932 Paul and Bunnell again stimulated interest by the introduction of the heterophile antibody reaction, which has proved to be a reliable diagnostic test. He agrees that the disease is prone to occur in the young but states that he has observed it in a husband and wife aged 62 and 58, respectively. The oldest patient seen by any of us was a man aged 44. Kracke considers the disease to be rare, or possibly even nonexistent, in Negroes, as he has never seen a patient with such a condition in the large Negro population of the Grady Hospital in Atlanta, Ga. There is evidence that it has a worldwide prevalence. Apparently there is no seasonal incidence. Although clinically the disease appears to be infectious, there are no confirmed studies which have demonstrated the

²⁶⁰ Bernstein, A. Infectious Mononucleosis, *Medicine* **19** 85, 1940

²⁶¹ Kracke, R. R. Infectious Mononucleosis, *Texas State J. Med.* **36** 348, 1940

causative organism It has been claimed that monkeys can be inoculated successfully with material from infected lymph nodes In 1 research worker the disease developed after he pricked his finger with an infected knife blade Nyfeldt isolated an organism which he called "*bacillus monocytogenes hominis*" and claimed that this agent will produce the condition in dogs Later Schmidt and Nyieldt reported that they obtained the same organism from the spinal fluid in 4 out of 5 patients At present it must be considered that the etiologic agent is unknown It may possibly be a virus Washings from the nasal cavities and throats of patients with the active disease failed to transmit it when sprayed into the throats of healthy persons The usual clinical manifestations are described in this article, and the occurrence of the meningeal type, with an increase in lymphocytic cells of the spinal fluid, is mentioned The prominence of abdominal pain as the leading symptom in some cases is emphasized, this symptom is attributed to swelling of the lymph glands in the mesenteric region, which has been observed at operation Infectious mononucleosis is almost always a febrile disorder, with an increase in temperature which persists usually for one to two weeks and has an average duration of eight to twelve days Of greatest importance in the diagnosis is the presence of enlarged and tender lymph glands preceding or following the onset of the fever It is believed by the author that the greatest increase in lymph glands is associated with the highest leukocyte count The spleen is moderately enlarged in 50 per cent of the cases In 1 instance splenic enlargement which extended to the umbilicus was noted In rare instances jaundice, which Kracke attributes to "intrahepatic obstruction," may be present The typical finding in the blood is an increase in the white cells to from 10,000 to 20,000 per cubic millimeter, with a relative and absolute lymphocytosis The most important diagnostic evidence of the disease is the unusual type of circulating lymphocyte The characteristic cell is described as a large, atypical, irregularly lobulated lymphocyte having sky blue cytoplasm with a clear perinuclear zone One of the outstanding features of this cell is the presence of small, variable-sized vacuoles which "almost stamps it without question as being a cell of infectious mononucleosis" The percentage of these unusual cells may be as high as 90, and in nearly all cases it exceeds 50 Kracke agrees that they are lymphoid in type and that their origin is probably from the involved lymphoid tissue and the spleen It is emphasized that the red cell count and the hemoglobin content are usually normal, a valuable differential point between this disease and leukemia

The heterophile antibody test is considered to be one of great reliability, as it established with certainty, in nearly all instances, the presence or absence of the disease He considers a titer of 1:32 as diagnostic and states that the reaction is almost always positive early

in the course of the disease. Although we consider that this test is an exceedingly valuable one, not this much reliance is placed on it, as in our experience the reaction is often negative early in the course of the disease. It is stated that the condition may be confused with leukemia, agranulocytosis and thrombopenic purpura. Because of the enlarged glands, and particularly the positive Wassermann and Kahn reactions in some cases, it must be differentiated from syphilis. Also, various syndromes characterized by enlarged glands, such as Hodgkin's disease, tuberculosis and lymphosarcoma, should be considered. In some cases there may be a rash, easily confused with the ordinary exanthems. The author states that there is no specific treatment for the condition and that it usually runs its course in about two weeks.

Grove²⁶² emphasizes that infectious mononucleosis is so frequently associated with symptoms and signs involving the upper respiratory tract that it should be kept constantly in mind by the laryngologist. About three fourths of the patients have some evidence of infection of the throat, the most frequent being injection of the pharynx, hypertrophy of the lymphoid tissue and, occasionally, membrane formation. When the disease is not ushered in with the symptoms of sore throat, the initial evidences are those of influenza or of cold in the head, with a febrile reaction. An almost constant clinical finding is enlarged glands, which are most frequently present in the anterior triangle of the neck. These may persist for a long time after the patient has recovered from other symptoms. They are never known to suppurate. It is emphasized that the diagnosis can usually be made with certainty at some time during the course of the disease when the symptoms are considered along with the changes in the blood and the development of the positive heterophile antibody reaction. The laryngologist should differentiate lesions of this condition from other membranous and ulcerative lesions affecting the pharynx, such as those of diphtheria, Vincent's angina, streptococcic sore throat, agranulocytosis, syphilis and tuberculosis. The author sounds a warning against the indiscriminate use of sulfanilamide in treating this condition, as the drug may have a tendency to depress further the number of granulocytes in the circulating blood. Cases are cited to emphasize that relapses may occur after apparent complete recovery, that convalescence is slow and protracted in some cases and that the atypical lymphocytes may be present in the blood stream for many weeks after the total white cell count has returned to normal. Furthermore, the glandular enlargement may not subside for many months, and the heterophile antibody reaction may continue to be positive for fifty to two hundred and ninety days after the subsidence of the clinical signs.

262 Grove, W. E. Laryngologic Aspects of Sporadic Infectious Mononucleosis, *Arch Otolaryng* **32** 472 (Sept.) 1940

Hollander²⁶³ has based his method of performing the heterophile antibody test on the principle that centrifugation offers a rapid and reliable technic for all agglutination tests. He centrifuges the mixture of sheep cells and human serum for five minutes at 1,000 revolutions per minute and, after shaking, reads for agglutination. It is claimed that in the high dilutions there is a greater sensitivity of the reaction with this method. Its greatest superiority, however, is due to the rapidity with which it can be performed. Such a rapid method will certainly be welcomed by the clinician.

According to Fowler and Tidrick,²⁶⁴ there is a renewed interest in infectious mononucleosis on account of the increasing use of the Paul-Bunnell heterophile antibody test. The diagnosis is made more frequently because of this aid and because attention is focused on the disease. It is becoming increasingly apparent that there are many cases in which atypical clinical pictures are presented and that there are many pitfalls in making the diagnosis. The characteristic clinical picture is described, with which account we are in accord, except for the statement which implies that the spleen is palpable in all patients. In our experience it has been palpable in about 50 per cent or less. Emphasis is placed on the prolonged period of convalescence and on the important fact that for months, although symptomatic recovery may be complete, lymphadenopathy and splenomegaly may persist and abnormal lymphocytes may remain in the blood stream. It is emphasized that the blood picture is typical and that the characteristic change is the presence of atypical lymphocytes. A common error has been to confuse these lymphocytes with the "blast" cells of acute leukemia. Attention is directed to the occurrence of the false positive Wassermann reaction in cases of infectious mononucleosis and confusion of the condition with early syphilis. Jaundice in association with infectious mononucleosis has been previously noted, and it is emphasized that the heterophile antibody test is of great value in the differential diagnosis. It is not improbable that many cases of so-called catarrhal jaundice have actually been ones of infectious mononucleosis. The highest agglutination titer for heterophile antibodies encountered by the authors has been 1:3,584, which was reduced to 1:112 by absorption with fresh guinea pig kidney. In this case, on account of the unusually high absorption with guinea pig kidney in the test, a lymph node was removed, and this showed hyperplasia compatible with infectious mononucleosis. It is properly emphasized that the heterophile antibody test with its recent modifi-

263 Hollander, A. Centrifuge Technique in Heterophile Agglutination Test, *J Lab & Clin Med* **25** 542, 1940.

264 Fowler, W. M., and Tidrick, R. T. Unusual Manifestations of Infectious Mononucleosis, *Am J Clin Path* **10** 548, 1940.

cations is of such accuracy that atypical cases can be recognized. If attention is directed toward the disease so that more complete hematologic and serologic tests are done on patients with enlarged lymph glands, obscure fever and symptoms of an infection of the upper respiratory tract, a greater recognized incidence of the condition will undoubtedly result.

Lassen and Thomsen ²⁶⁵ state that the various clinical pictures which infectious mononucleosis presents are linked together by the characteristic blood changes and the heterophile antibody reaction, thereby forming a well defined nosographic unit, although the etiologic agent is unknown. Until recent years the treatment has been entirely symptomatic, as the disease has been considered benign, with a duration which does not exceed three weeks. More recently, however, it has been appreciated that the condition may be accompanied by a severe and sometimes necrotic angina and that symptoms may persist for several months. Moreover, it has been recognized recently that there is a meningeal type, characterized by headache, rigid neck, mental symptoms, transient paralysis, paresthesias and increased cell content of the spinal fluid. The work of Thomsen and Vinttup is cited, in which 6 cases of fatal infectious mononucleosis were reported. It was shown that the process may localize, apparently selectively, in the respiratory center and there produce paralysis, with a fatal termination. The same authors also showed in studying over 500 cases from Blegdam Hospital, Copenhagen, Denmark, that the mortality rate is between 1 and 2 per cent. Lassen and Thomsen cite Anderson's report of 2 cases of fatal termination in Denmark. According to the authors, it is "rather probable" that more severe forms of the disease have been regarded in the past as septic angina, malignant diphtheria, meningitis or encephalitis. It is their opinion that the serologic test will afford the means of proving that the disease occasionally has a more unfavorable prognosis. In 12 cases of the most severe form treatment was with 30 to 300 cc of convalescent serum. The results were compared with the outcome in 15 cases of severe disease in which no treatment was given, 50 cases in which nonspecific serum was used and 27 cases in which intravenous injections of neoarsphenamine were given. In those cases in which treatment was with convalescent serum there was a rapid improvement in the general condition of the patients. The body temperature fell to normal within twenty-four to forty-eight hours, and the patients had a "pronounced feeling of detoxication." In other cases sulfanilamide therapy was used, but results of this treatment will be the subject of another report. The only other reference, and this was favorable, to

²⁶⁵ Lassen, H. C. A., and Thomsen, S. Treatment of Infectious Mononucleosis with Specific Convalescent Serum, *Acta med. Scandinav.* **104**: 498, 1940.

the use of convalescent serum in the treatment of the disease is the report of Whitby and Britton, in 1939²⁶⁶

According to Gall and Stout,²⁶⁷ a survey of the literature reveals that there is no consistent lesion reported to be found in the lymph glands of patients with infectious mononucleosis. The authors removed nodes from 10 patients with the disease. They describe changes which occur with such regularity, and with such infrequency in other conditions, that they believe them to be of diagnostic significance. The picture they describe is characterized not by a single pathologic feature but by a general pattern and change in the node. The gross architectural relationships are retained, the basic process underlying the lesion is essentially the result of proliferative stimulation of the components of the nodes, the "infectious mononucleosis cells," similar to those observed in the circulating blood, are seen in the lymph nodes in small numbers, such cells are large, two or three times the size of a small lymphocyte, and have abundant basophilic cytoplasm, either granular or rather coarsely vacuolated. For the finer details of the pathologic changes and a review of the literature, reference should be made to the original article.

Robinson²⁶⁸ describes the case of a man aged 29 in whom developed vague symptoms which were eventually recognized as evidence of infectious mononucleosis. This case was regarded as sporadic until further investigations indicated that there had probably been at least 3 other cases which had been overlooked. This is a situation which undoubtedly occurs frequently. A case should not be called sporadic until a careful investigation has eliminated the possibility that other cases have not been recognized.

Chapman and Chapman²⁶⁹ report 7 cases of infectious mononucleosis in children and young adults, in all of whom jaundice developed a few days after the onset of symptoms. In all, the peripheral blood showed cells typical of those occurring in infectious mononucleosis. This finding, when considered with the generalized enlargement of lymph glands and such evidence of infection as fever, led the observers to conclude that they were dealing with infectious mononucleosis. The heterophile antibody reaction was not determined in any of the cases, as the facilities were not available. It was concluded that the jaundice was of the

266 Whitby, L. E. H., and Britton, C. J. C. *Disorders of the Blood*, ed 3, Philadelphia, The Blakiston Company, 1939.

267 Gall, E. A., and Stout, H. A. Histologic Lesion in Lymph Nodes in Infectious Mononucleosis, *Am J Path* **16** 433, 1940.

268 Robinson, J. B. Infectious Mononucleosis. Report of Case, *Chinese M J* **57** 473, 1940.

269 Chapman, A. A., and Chapman, J. Infectious Mononucleosis with Jaundice, *Southwestern Med* **24** 200, 1940.

obstructive type but that it was incomplete, as the stools were not clay colored. The obstruction might have been partially due to pressure from an enlarged lymph node in the region of the common duct. It is stated, however, that it is equally permissible to consider the jaundice as being due to toxic hepatitis, an explanation which we favor.

Haines and Corn²⁷⁰ present the case of a girl aged 13 in whom the usual symptoms of infectious mononucleosis developed. On the following day her brother became ill with all of the evidences of scarlet fever. Both were given convalescent scarlet fever serum. Within two days the boy's temperature became normal, but the girl's rose to 104 F. At this time there was redness of the pharynx but no membrane or edema of the throat. There was a suggestion of strawberry tongue. The cervical lymph nodes were enlarged, discrete and tender. There was a diffuse erythematous flush. Five grams of sulfanilamide was given over a period of three days, without material effect on the course of the disease, as the patient continued to have a septic fever for eight days despite the medication. Examination of the blood eighteen days after the onset showed a white cell count of 14,900 per cubic millimeter. The differential count revealed that 88 per cent of the leukocytes were large lymphocytes typical of infectious mononucleosis. The red cells showed rather remarkable evidence of regeneration, as indicated by polychromatophilia, basophilic stippling and the presence of an occasional normoblast. The hemoglobin percentage and the erythrocyte count were not stated. Also, occasional promyelocytes and myelocytes were seen, as well as a rare cell which was interpreted to be a "leukoblast." The heterophile antibody reaction was reported positive in a dilution of 1:150. The patient made a complete recovery and remained well until eighteen days later, when acute suppurative appendicitis developed, a diagnosis confirmed by operation. At this time her leukocyte count was 18,300 per cubic millimeter, with a differential count of 45 per cent lymphocytes, 7 per cent monocytes and 48 per cent polymorphonuclears. The case was reported because the blood picture varied from that usually observed in infectious mononucleosis, as there were anemia, evidence of red blood cell regeneration and a mild leukemoid reaction. It was suggested that these changes were due to the administration of sulfanilamide.

Priestley²¹⁸ reports the case of a woman aged 25 who had the syndrome of thrombopenic purpura for which a splenectomy was performed uneventfully. Two weeks after the operation fever developed, with a number of swollen tender glands in the neck, axillae and groins. The fever, which was of the remittent type, was present for several

270 Haines, D. J., and Corn, H. H. Infectious Mononucleosis with Mild Leukemoid Reaction. Report of Case, *J. Iowa M. Soc.* 30:430, 1940.

weeks About one week after the onset of the fever, the white blood cell count was 10,200 per cubic millimeter, with 52 per cent neutrophils, 25 per cent lymphocytes, 3.5 per cent monocytes, 2 per cent eosinophils, 2 per cent basophils and 15.5 per cent unclassifiable mononuclear cells The Paul-Bunnell reaction was negative About ten days later the white blood cell count was 15,950 per cubic millimeter, and of these 74 per cent were lymphocytes The author states that the mononucleosis was difficult to explain and the diagnosis of infectious mononucleosis was made only by the successive elimination of the various forms of pyrexia associated with enlargement of the cervical lymph nodes With the available evidence it was thought that this diagnosis was most probable, despite the negative Paul-Bunnell reaction

Kent²⁷¹ reports the case of a boy aged 14 who had acute leukemia, probably of the monocytic type, in which the heterophile antibody reaction was positive in a titer of 1:4,096 when the original technic of Paul and Bunnell, described in 1932, was employed There does not seem to be any doubt concerning the diagnosis of acute leukemia, but, as is often the case, a difference of opinion arose as to whether it was monocytic or myelogenous The hemoglobin concentration was 42 per cent, the red blood cell count 2,110,000 per cubic millimeter and the white blood cell count 20,900 per cubic millimeter, with 82 per cent immature unclassified cells (many resembled monocytes and others myelocytes) The patient had received neoarsphenamine intravenously and sulfanilamide orally No horse serum had been given It is important that such a case as this be reported because the heterophile antibody reaction is recognized as one of the most reliable means of differentiating the various types of leukemia from infectious mononucleosis Certainly it is rarely positive in cases of the leukemias There is no statement in the case history concerning the parenteral use of liver extract, which may well have been given in a case of this type According to Bernstein²⁶⁰ this treatment may result in the reaction becoming positive

HODGKIN'S DISEASE

A comprehensive review of the symptomatology of Hodgkin's disease has been made by Goldman,²⁷² who analyzed 212 cases The disease occurred at any age but was most prevalent during the third decade The ratio of males to females was about 2:1 Hodgkin's disease was noted in every race, and no predisposing factors were observed The most common symptoms were lymphadenopathy, loss of weight and

271 Kent, C. F. "False" Positive Paul-Bunnell (Heterophile) Reaction? *Am J Clin Path* **10** 576, 1940

272 Goldman, L. B. Hodgkin's Disease Analysis of Two Hundred and Twelve Cases, *J A M A* **114** 1611 (April 27) 1940

weakness, pruritus and dyspnea. The enlarged glands varied in size and number. At the onset lymphadenopathy was usually unilateral. The spleen was rarely enlarged until late in the course of the disease. Hoarseness occurred in about 6 per cent of the cases. Owing to the rapid enlargement of the mediastinal glands and pressure on the veins, effusion was common. In other types of mediastinal tumors, growth is usually slow and distention of superficial veins is more common. Roentgenograms were considered of little value in the differentiation of the various mediastinal masses.

Involvement of the skin was noted in 38 per cent of the cases. Pruritus, infiltration of the skin and exfoliative dermatitis were most common, only occasionally was herpes zoster present. Bone disease was noted in 66 per cent of the cases, and 10 instances of transverse myelitis were found.

It is especially to be noted that there was no characteristic blood picture. Usually there was leukocytosis, with a relative and an absolute increase in granulocytes and monocytes and a corresponding decrease in lymphocytes. Eosinophilia was observed in 20 per cent of the cases. Some degree of anemia was often observed. Fever of the continuous type was most common, the Pel-Ebstein type of fever was rare.

The average duration of life was thirty-two and six-hundredths months. The shortest course observed was two and a half months, and the longest, eleven years. Following treatment, the average duration of life was twenty-three and eight-tenths months. Ten per cent of the patients lived for five years or more.

Baker and Mann²⁷³ reported 65 cases of a condition proved by biopsy or autopsy to be Hodgkin's disease. In 47 cases the patients were males and in 18 females. The disease occurred most often during the second and third decades. In only 1 case was there associated tuberculosis, and the authors state that there is no proved relationship between the two diseases. Adenopathy was observed in every case at some time during the course of the disease, and usually the cervical glands were involved. Splenomegaly occurred in one half of the cases. Fever was not common if only the superficial glands were affected. The average survival period was about eighteen months. Death was often due to associated anemia, pulmonary disease or involvement of the central nervous system.

Levitt and Weisman²⁷⁴ analyzed 29 cases of Hodgkin's disease. With minor variations, their findings are in agreement with the previously described observations. These authors especially emphasize the value of roentgen therapy and cite figures to prove the prolongation of life with

273 Baker, C., and Mann, W. N. Hodgkin's Disease, *Lancet* **1** 23, 1940.

274 Levitt, A., and Weisman, S. J. Hodgkin's Disease. Case Series Analysis, *M. Times*, New York **68** 315 1940.

this type of treatment. If the patients had roentgen therapy the average duration of life was twenty-eight and eight-tenths months, without such treatment the average duration of life was only seven and six-tenths months.

Case reports describing various atypical aspects of Hodgkin's disease are numerous. Lisa²⁷⁵ cites the case of a 63 year old woman who had associated Raynaud's disease and herpes zoster. Osteopetrosis was observed for the first time by Herscher and Stein²⁷⁶. The authors point out that there is probably a hereditary factor, although a definite cause is not known. The disease is characterized by an excessive formation of bone, anemia and fibrosis of the liver, spleen and lymphoid tissue. Cabot case no 26062²⁷⁷ is concerned with the occurrence of Hodgkin's disease involving the retroperitoneal lymphoid tissue and the spleen. Infarction, with subsequent ulceration, of the spleen was observed. Perforation of the stomach resulted from direct contact. Craver and Sunderland²⁷⁸ cite a case of mistaken diagnosis of carcinoma of the stomach in which this condition had been reported cured by roentgen therapy. Actually the patient had Hodgkin's disease and carcinoma of the colon. Sayago²⁷⁹ points out that radium is seldom used and reports a case in which the patient was successfully treated with small quantities.

Special cultural technic for the isolation of brucella organisms is described by Poston and Parsons²⁸⁰. Employing this method, the investigators cultured glands from 19 patients with Hodgkin's disease. Ten cultures were positive for such organisms. Cultures of tissue from nodes of 3 patients with undulant fever were positive in every instance. From 67 nodes routinely examined, only 1 positive culture was obtained. Wise and Poston²⁸¹ demonstrated the coexistence of brucella infection and Hodgkin's disease in 14 consecutive cases by isolation of *Brucella*

275 Lisa, J. R. Neurologic Complications in Hodgkin's Disease, New York State J. Med. **40** 62, 1940.

276 Herscher, H., and Stein, J. J. Osteopetrosis Associated with Hodgkin's Disease. Review of Literature and Report of Case, Am. J. Roentgenol. **43** 74, 1940.

277 Hodgkin's Disease of Spleen and Retroperitoneal Tissues, Cabot Case 26062, New England J. Med. **222** 233, 1940.

278 Craver, L. F., and Sunderland, D. A. Hodgkin's Disease and Carcinoma of the Colon. Mistaken Diagnosis of Carcinoma of the Stomach, J. A. M. A. **114** 1623 (April 27) 1940.

279 Savago, C. Radium Therapy in Hodgkin's Disease. Report of Case, Am. J. Roentgenol. **42** 888, 1939.

280 Poston, M. A., and Parsons, P. B. Isolation of *Brucella* from Lymph Nodes, J. Infect. Dis. **66** 86, 1940.

281 Wise, N. B., and Poston, M. A. Coexistence of *Brucella* Infection and Hodgkin's Disease. Clinical, Bacteriologic and Immunologic Study, J. A. M. A. **115** 1976 (Dec. 7) 1940.

melitensis from cultures of blood or lymph nodes. Apparently the authors used the same data as Poston and Parsons. In summarizing their work, Wise and Poston state that the results do not establish an etiologic relationship of brucella infection to Hodgkin's disease but suggest that the clinical course of Hodgkin's disease may be significantly influenced by brucella infection.

The properties of the encephalopathic agent (the Gordon body) present in the bone marrow of monkeys were investigated by King²⁸². He noted that it was readily soluble at a p_H of 7.4, as well as at a lower p_H of 2.0 or 3.0. The point of minimal solubility was a p_H of 4.2. The material was inactivated by a temperature of 75°C for fifteen minutes, it was digested by pepsin, it had a slight degree of sedimentation with an air-driven centrifuge, and it was nondialyzable. It was precipitated from a solution (p_H of 7.4) by ammonium sulfate, over a range of 0.4 to 0.8 saturation. These findings suggest that the reagent is a protein. This material was injected into guinea pigs, and the clinical and pathologic effects were studied. The latter effects depended on the number of Purkinje cells destroyed.

LYMPHOSARCOMA AND LYMPHOMATOID DISEASES

An extensive review of lymphosarcoma was recently published by Sugarbaker and Craver²⁸³. They define lymphosarcoma as a malignant neoplastic disease of lymphoid tissue capable of arising in any lymphoid aggregate. It may be acute or chronic and is usually radiosensitive. The outcome is fatal, owing to widespread metastasis. The disease is commonly termed malignant lymphoma, or lymphoblastoma.

Kundrat first recognized lymphosarcoma in 1893. Often it is difficult to classify the disease properly, owing to the varied pathologic manifestations. Two types are recognized, the reticulum type, or lymphosarcoma, and the lymphocytic type, or malignant lymphocytoma. In either there is a predominance of the particular cell, with subsequent obliteration of the follicular architecture, invasion of underlying tissues and outward growth of the tumor (invasion of the capsule and surrounding tissue).

The exact etiologic relations are not known, although the condition is considered to be malignant. Kirschbaum and his associates²⁸⁴ were able

282 King, L. S. Some Properties of the Encephalopathic Agent in Primate Bone Marrow (The Gordon Agent), *J. Exper. Med.* **71** 603, 1940.

283 Sugarbaker, E. D., and Craver, L. F. Lymphosarcoma. Study of One Hundred and Ninety-Six Cases with Biopsy, *J. A. M. A.* **115** 17 (July 6), 112 (July 13) 1940.

284 Kirschbaum, A., Gardner, W. U., Nahigian, R., and Strong, L. C. Differentiation Between Sarcomatous and Leukemic Lymphocytes in Mice, *Yale J. Biol. & Med.* **12** 473, 1940.

to differentiate between sarcomatous and leukemic lymphocytes by injecting the malignant cells into mice. When leukemic cells were injected, regardless of the site or route, there was widespread metastasis, with evidence in the blood stream. When lymphosarcomatous cells were injected under the skin, a localized tumor occurred, without any evidence in the peripheral blood. If cells of the latter type were injected intravenously, there were few "takes." The authors concluded that these results indicated differences in the pathologic processes of the two diseases.

Sugarbaker and Craver point out that lymphosarcoma is less common than Hodgkin's disease, the two occurring in the ratio of 3:4. Males are affected about twice as often as females. The former disease is rare before the age of 20 and after the age of 70, though it has occurred in younger and in older persons. The reticulum cell type predominates.

The initial sites involved, with associated symptoms, in the order of their frequency are lymphoid tissue, the upper respiratory tract, the mediastinum and bone. Cervical glands are usually affected first, then in order of frequency are axillary, inguinal, abdominal, mediastinal and epitrochlear glands. Generalized lymphadenopathy is rare. It is to be noted that during the course of the disease any organ or tissue may be affected.

There is no typical hemogram, and at the onset the blood is surprisingly normal. A definite diagnosis can be made only by biopsy.

Since lymphosarcoma is radiosensitive, roentgen irradiation is the therapeutic method of choice. The disease rarely recurs in the areas treated, although new evidence of it may be found elsewhere. Sugarbaker and Craver divided their cases according to the treatment given. In 49 per cent of the cases roentgen radiation alone was given, in 12 per cent radium or radon, in 13 per cent a combination of roentgen radiation and radium, in 12 per cent surgical treatment and in the remaining cases total irradiation was carried out, according to the method of Heublein. In an analysis of the results obtained with the various types of therapy, it appeared that in the early stages of the disease the combination of surgical treatment and roentgen irradiation was most effective. Later in the course of illness roentgen irradiation alone was the best treatment. The authors demonstrated that the most effective single dose was 400 to 600 and that not over 2,000 to 3,000 r per area should be given.

Of the group of patients that were followed throughout the course of illness, 15.9 per cent had a five year period of survival. In addition to roentgen therapy, other factors which influenced the course of the disease were individual inherent qualities, the extent of the disease on

admission to the hospital, the location of the primary lesion, the age of the patient and the presence or absence of complications

Owen²⁸⁵ cites a case of infection with torula which was mistaken for lymphosarcoma. He advises that cultures be made of all material taken for biopsy. From our experience, we are definitely in agreement that fungous infections may clinically simulate lymphoblastoma. It is pointed out by Loveman²⁸⁶ that lymphosarcoma of the skin may occur long before there is any evidence in the lymph glands. The author emphasizes the importance of making a clinical diagnosis and especially denounces the terminology. A case of leukemia of the skin was reported by Caird²⁸⁷ as one of chloroma. No true chloroma tumors were found, and from the evidence submitted, the most likely diagnosis is myelogenous leukemia. Lehman and Leaman²⁸⁸ describe a typical case of Mikulicz' disease occurring in a 55 year old woman. They point out that the disease is benign and should be differentiated from Mikulicz' syndrome, which has a grave prognosis.

Giant follicular lymphadenopathy was first described by Brill, Baehi and Rosenthal, in 1925. As noted by Baggenstoss and Heck,²⁸⁹ the disease has been recognized more frequently in recent years. These investigators report 13 cases, in 7 of which the patients died. Three necropsies and 8 biopsies were performed. The disease is characterized by an insidious onset, with regional or generalized lymphadenopathy, splenomegaly, normal blood and marked radiosensitivity of the lesions. The average duration of life was four and a half years, though 2 patients survived for seventeen years. The pathologic picture is characteristic, but it is often difficult to distinguish from that of lymphoblastoma or inflammation.

Powell²⁹⁰ presents 2 cases of giant follicular hyperplasia and recommends roentgen therapy. Salm²⁹¹ also describes 2 cases of this disease and expresses the belief that it is a prelymphoblastoma stage. Although

285 Owen, M. Generalized Cryptococcosis Simulating Hodgkin's Disease, *Texas State J Med* **35** 767, 1940.

286 Loveman, A. B. Reticulocytoblastoma Cutis (Nonleukemic Malignant Reticulo-Endotheliosis). Report of a Case, *Internat Clin* **4**:163, 1940.

287 Caird, J. C. Case Record—Chloroma, *Edinburgh M J* **47** 762, 1940.

288 Lehman, J. A., and Leaman, W. G., Jr. Mikulicz' Disease, *Internat Clin* **3** 105, 1940.

289 Baggenstoss, A. H. and Heck, F. J. Follicular Lymphoblastoma (Giant Lymph Follicle Hyperplasia of Lymph Nodes and Spleen), *Am J M Sc* **200**: 17, 1940.

290 Powell, C. Giant Follicular Lymphadenopathy, *Canad M A J* **42** 372, 1940.

291 Salm, R. Two Cases of Follicular Lymphoblastoma, *Edinburgh M J* **47** 486, 1940.

Salm's opinion is in agreement with that of most authors, there are many who consider giant follicular lymphadenopathy to be a benign disease

LEUKEMIA

Leukemia, according to Jackson,²⁹² may be defined as an acute or chronic systemic disease involving primarily the blood-forming organs, it is characterized by widespread, disorderly and profitless proliferation of the leukocytes and their precursors, manifest by the presence, often in large numbers, of immature or abnormal white cells in the peripheral blood stream. In the vast majority of cases it leads to death within a comparatively short time. Jackson classifies leukemias in three groups, the myelogenous and lymphatic forms, which may be acute or chronic, and the monocytic form, which is usually acute.

Many interesting observations related to leukemia have been reported by Jackson. In a total of 8,693 autopsies, there were 78 instances of leukemia, of a total of 324,785 patients admitted to the hospital, leukemia was noted in only 333. The disease was more common in men. Acute leukemia was usually seen in younger persons. Chronic myelogenous leukemia was most common in the second and third decades, and lymphatic leukemia occurred in a later age group (45 to 60 years). The patients often exhibited symptoms of increased metabolism and of hemorrhage, negative nitrogen balance was not unusual, and myelophthisic anemia was common. In addition to the blood-forming organs, the areas most often involved were the mouth and pharynx, eyes, central nervous system, skin and bones.

Jackson stated that the onset in acute leukemia is insidious or abrupt, usually occurring in infancy or childhood. The symptoms vary. The signs may be absent at the onset, abnormal white cells are always present in the peripheral blood, although the actual white cell count may be increased or decreased, anemia is always present, and the platelets are decreased. The course is rapidly downhill. Transfusions are only palliative, and roentgen therapy is contraindicated.

Chronic myelogenous leukemia is characterized by an insidious onset, symptoms and signs of increased metabolism, abdominal discomfort, cardiorespiratory symptoms and pain in the left upper quadrant of the abdomen. Physical examination reveals pallor and splenomegaly. The predominant findings in the blood are anemia, abnormal myeloid cells in the circulation and a decreased number of platelets. Treatment recommended includes roentgen irradiation, blood transfusion and administration of solution of potassium arsenite. U S P.

Chronic lymphatic leukemia is relatively benign. The outstanding sign is generalized lymphadenopathy. The blood picture differs from

292 Jackson, H., Jr. Leukemias, *New England J. Med.* **222** 22, 1940

that in myelogenous leukemia only in that the lymphoid series predominates. Here again, roentgen irradiation and transfusions are suggested as the treatment of choice.

Caird²⁹³ describes 5 cases of leukemia of the acute type, emphasizing the signs and symptoms, and points out that leukopenia is usually present. Stransky and Quintos²⁹⁴ stress the alterations that occur in the bone marrow of leukemic patients and are of the opinion that these are most important in differentiating the leukemias. Sixteen cases of myeloblastic leukemia are reported by Tischendorf and Herzog²⁹⁵. They point out the difficulties encountered in the differential diagnosis and state that the acute and subacute forms of leukemia are variations of the chronic type. It is their opinion that leukemia is a neoplastic disease.

The clinical and hematologic aspects of acute leukemia have been analyzed by Piney²⁹⁶. The disease is characterized as fulminating from the onset, more common in males and rare after the second decade. Pallor is severe, and swelling and ulceration of the gums are common as is fever. Lymphadenopathy and splenomegaly are usually present, although not necessarily so. The course is rapidly downhill, with death occurring in six to eight weeks. According to the author, an atypical form of the disease is frequently observed and can be readily recognized by studies of the bone marrow.

Wintrobe and Mitchell²⁹⁷ discuss the atypical manifestations which may occur in the various types of leukemia. It is their belief that any and every organ may be involved, whether or not clinical signs are present, and therefore the possibility of the disease must be kept in mind at all times, regardless of the presenting symptoms. These authors are in agreement with the consensus that the study of the bone marrow is most helpful in establishing a diagnosis.

A case of acute eosinophilic leukemia, occurring in a 5 year old boy, is reported by Reye²⁹⁸. The patient had a severe anemia, and the differential count revealed more than 70 per cent eosinophils. Death

293 Caird, J. C. Early Stages of Leukaemia, *Edinburgh M. J.* **47** 264, 1940.

294 Stransky, E., and Quintos, F. N. Differential Diagnosis of Leucemia, *J. Philippine M. A.* **20** 267, 1940.

295 Tischendorf, W., and Herzog, K. Mehrjährige Beobachtungen über chronische Leukämien und Polycythämien, *Deutsches Arch. f. klin. Med.* **185** 566, 1940.

296 Piney, A. Acute Leukemia. A Clinical and Haematological Study, *Edinburgh M. J.* **47** 616, 1940.

297 Wintrobe, M. M., and Mitchell, D. M. Atypical Manifestations of Leukaemia, *Quart. J. Med.* **9** 67, 1940.

298 Reye, D. Case of Acute Eosinophilic Leukaemia, *M. J. Australia* **2** 156, 1940.

was due to cardiac failure resulting from multiple cardiac infarcts. The author was unable to account for the eosinophilia, hence termed the condition "eosinophilic leuchaemia."

Lepak²⁹⁹ observed a 41 year old man with tuberculosis in whom an enlarged spleen and liver developed, with a blood picture simulating leukemia, the majority of the cells being of the eosinophilic type. In the author's opinion, the diagnosis of eosinophilic or basophilic leukemia is extremely difficult to make, as immature cells of these types are rarely present in the peripheral blood.

The occurrence and frequency of oral manifestations in cases of acute leukemia are stressed by Moloney³⁰⁰. Of a series of 152 cases of acute leukemia, oral lesions were present in more than half. The pathologic lesions are mainly limited to the gingival tissues and are characterized by bleeding and infiltration of the gums, which are swollen and painful. Ulcerations and necrosis are commonly present. The author also emphasizes the fact that oral surgical treatment is contraindicated.

Hauptman and Taussig³⁰¹ reported a case in which there was infiltration of the female internal genitalia with cells characteristic of leukemia. Although the condition is extremely rare, the authors are of the opinion that this type of neoplastic invasion should always be considered as a possibility in cases of unexplained vaginal bleeding.

Murphy and Brody³⁰² discuss the occurrence of involvement of the central nervous system in myelogenous leukemia. The usual pathologic manifestation is a localized collection of abnormal white cells in the meninges. Less commonly, there is invasion of the spinal and cranial nerve roots by myeloid elements. A case illustrating the latter type of pathologic lesion is reported by the authors.

The bone changes which may occur in leukemia are classified by Mendl and Saxl³⁰³ as follows: (1) local proliferation in the bone marrow with erosion of the cellular trabeculae and subsequent forma-

299 Lepak, J. A. Eosinophilic Hyperleucocytosis. Eosinophilic Leukemia or Myelogenous Leukemia with Case Report with Discussion of Medical Literature, *Minnesota Med* **23** 596, 1940.

300 Moloney, W. C. Clinical Significance of Oral Lesions in Acute Leukemia, *New England J Med* **222** 577, 1940.

301 Hauptman, H., and Taussig, F. J. Leucemic Infiltration of the Female Internal Genitalia as Cause of Vaginal Bleeding, *Am J Obst & Gynec* **39** 70, 1940.

302 Murphy, J. P., and Brody, B. S. Nerve Root Infiltration in Myelogenous Leukemia, *J A M A* **115** 1544 (Nov 2) 1940.

303 Mendl, K., and Saxl, O. Bone Changes in Leukemia, *Am J Roentgenol* **44** 31, 1940.

tion of a central cavity, (2) periosteal proliferation, and (3) sclerosis surrounding the area of cavity formation. Three cases illustrating the bone changes are presented by the authors, who state that roentgenologic evidence alone is not sufficient basis for diagnosing leukemic destruction of bone.

Neal³⁰⁴ reports the case of a 44 year old man with myelogenous leukemia who died as a result of a ruptured spleen. This complication, the author states, is extremely rare. Another rare complication of myelogenous leukemia, according to Jones,³⁰⁵ is infiltration of the small intestine. He observed a case in which there was extensive ulceration of the small intestine at the site of infiltration. The ulcer perforated and caused generalized peritonitis.

Bauer and McGavack³⁰⁶ call attention to the uncommon association of leukemia and diabetes mellitus. Only 16 cases in which the two diseases existed together have been previously reported. They believe that the rarity is due to (1) unreported cases, (2) prevention or modification of the course of diabetes by leukemia, and (3) prevention or modification of the course of leukemia by diabetes.

Blum and Combs³⁰⁷ observed a case of lymphatic leukemia complicated by pneumococcal pneumonia type III and successfully treated with sulfapyridine and serum. They express the opinion that the drug can be administered to patients with such conditions if it is given with the usual precautions.

Two cases of monocytic leukemia, substantiated by the changes in blood and bone marrow, but not by autopsy observations, were reported by Hsiang³⁰⁸. Watkins and Hall³⁰⁹ observed 29 cases of monocytic leukemia, 23 were of the Nageli type and 6 of the Schilling type. The authors believe the two types may be differentiated by the characteristics of the predominant cell and its progenitors and by the histopathologic changes in the hematopoietic tissues. In their opinion the Nageli type

304 Neal, J. M. Rupture of Spleen in Myelogenous Leukemia, *M. Bull. Vet. Admin.* **17** 96, 1940.

305 Jones, E. I. Intestinal Ulceration in Myelogenous Leukemia, *Lancet* **1** 174, 1940.

306 Bauer, H. G., and McGavack, T. H. Leukemia and Diabetes Mellitus. Report of Case, *Bull. New York M. Coll., Flower and Fifth Ave. Hosps.* **3** 7, 1940.

307 Blum, L. L., and Combs, S. R. Case Report. Chronic Lymphatic Leukemia Complicated by Type III Pneumococcus Pneumonia, Recovery from Pneumonia with Sulfapyridine and Serum, *J. Indiana M. A.* **33** 424, 1940.

308 Hsiang, H. T. Acute Monocytic Leukaemia. Report of Two Cases in Chinese, *Chinese M. J.* **57** 240, 1940.

309 Watkins, C. H., and Hall, B. E. Monocytic Leukemia of the Nageli and Schilling Types, *Am. J. Clin. Path.* **10** 387, 1940.

is a variant of myelogenous leukemia and the Schilling type a variant of leukemic reticuloendotheliosis

Ulrich and Parks³¹⁰ observed a patient with tuberculosis and a leukemoid reaction in the peripheral blood. At autopsy, the bone marrow was leukemic without any evidence of tuberculosis, which, however, was present in other parts of the body. The authors are of the opinion that tuberculosis may be latent and activated by leukemia or may be contracted, as a result of the patient's poor condition.

Aleukemic leukemia is considered by Hynes³¹¹ to be a variant of acute leukemia. He points out that in many ways it may resemble lymphosarcoma leukemia. Hynes cites many cases to illustrate his theory. Bates and Haine³¹² describe a case of aleukemic leukemia in a 4 year old boy. The outstanding feature was widespread metastasis, especially in the subcutaneous tissues and muscles. A case of questionable aleukemic leukemia with a duration of life of twenty-five years is reported by Burgess³¹³. Sinclair³¹⁴ observed a 23 year old woman with aleukemic leukemia. Biopsy of a node revealed the presence of undifferentiated pale cells, which were suggestive of a neoplasm.

Jackson and his colleagues³¹⁵ describe a syndrome (agnogenic myeloid metaplasia of the spleen) which simulates leukemia and report 10 cases. The common symptoms were weakness, abdominal distress and hemorrhage. Physical examination revealed splenomegaly. The blood picture was that of a leukemoid reaction. Microscopic sections of the spleen showed marked myeloid metaplasia and scattered foci of immature red and white blood cells and megakaryocytes distributed throughout a slightly or markedly fibrosed spleen. At autopsy, similar ectopic blood formation was present in the liver and the lymph nodes. The bone marrow was variable in consistency, exhibiting at times fibrosis, hyperplasia or aplasia. On some occasions no pathologic change was noted. The authors emphasize the fact that a proper clinical diagnosis must be made in order that no unnecessary treatment be given. According to the cases described by the investigators, roentgen therapy shortens the duration of life.

310 Ulrich, H, and Parks, H. The Relation Between Leukemia and Tuberculosis. Report of Case, *New England J Med* **222** 711, 1940

311 Hynes, M. Aleukaemic Leukaemia, *Quart J Med* **9** 177, 1940

312 Bates, I, and Haine, G. L. Aleukaemic Lymphadenosis with Extensive Subcutaneous Deposits, *Lancet* **1** 917, 1940

313 Burgess, A. M. Lymphatic Leukemia with "Aleukemic" Stage of Unusually Long Duration, *Rhode Island M J* **23** 26, 1940

314 Sinclair, C. W. Aleukaemic Leukaemia, *M J Australia* **2** 517, 1940

315 Jackson, H., Jr., Parker, F., Jr., and Lemon, H. M. Agnogenic Myeloid Metaplasia of Spleen. Syndrome Simulating Other More Definite Hematologic Disorders. *New England J Med* **222** 985, 1940

Kimura and his co-workers ¹⁶ report 5 cases of leukanemia with autopsy observations. It is to be noted that these workers use the term leukanemia to designate a leukemoid blood reaction. A case of acute suppurative pericarditis with an initial leukemoid blood picture in which treatment was successful has been observed by Wolfson and Sharpe ¹⁷.

The configuration of glutamic acid isolated from leukemic tissue proteins was studied by Arnow, Opsahl and Watson ¹⁸. They were unable to detect the presence of any racemic glutamic acid. Turner and his co-workers ¹⁹ noted that of 12 cases of myelogenous leukemia the iodine content of the blood was abnormally low in 9 and normal in 3. Of 17 cases of lymphatic leukemia, it was elevated in 41 per cent and normal in 59 per cent. As pointed out by the investigators, there was no overlapping of the two groups.

The treatment of leukemia, generally speaking, is unsatisfactory. According to the "Conferences on Therapy," ²⁰ rest and regulation of activity are indicated, no special diet is necessary, although the patients may have to change their eating habits, owing to pressure symptoms, proper oral hygiene should be maintained, a change of climate is of no value, surgical treatment may be given, with reluctance, under strict supervision, transfusions are only palliative, solution of potassium arsenite U S P and benzene may be helpful, and roentgen irradiation may be beneficial in selected cases. In regard to transfusions, some authorities are of the opinion that they should not be given.

It is to be remembered that roentgen irradiation is only palliative and rarely, if ever, alters the course of the disease. Decision to use roentgen therapy will depend on the white blood cell count, the type of abnormal white blood cells in the circulation and the symptoms and signs present. Roentgen irradiation is contraindicated in cases of acute leukemia, leukopenia (if produced by roentgen rays or drugs), thrombo-

316 Kimura, S., Hiraga, S., and Kumagai, K. Five Cases of Acute Myelosis in Childhood, Including Two Cases of So-Called Leukanemia, *Tohoku J. Exper. Med.* **38** 414, 1940.

317 Wolfson, M., and Sharpe, J. C. Acute Suppurative Pericarditis with an Initial Leukemoid Blood Picture, *California & West Med.* **52** 116, 1940.

318 Arnow, L. E., Opsahl, J. C., and Watson, C. J. Configuration of Glutamic Acid Isolated from Subacute Lymphatic Leukemic Tissue Proteins, *Proc. Soc. Exper. Biol. & Med.* **43** 766, 1940.

319 Turner, K. B., DeLamater, A., and Province, W. D. Observations on the Blood Iodine. I. The Blood Iodine in Health, in Thyroid and Cardiorenal Disease and in Leukemia, *J. Clin. Investigation* **19** 515, 1940.

320 Conferences on Therapy (from Cornell University Medical School and New York Hospital). The Treatment of Blood Disorders, The Use of Transfusions, *J. A. M. A.* **114** 2375 (June 15) 1940. Roentgen Therapy, *ibid.* **114** 2451 (June 22) 1940. Conferences on Therapy ²⁵⁹.

penia and pregnancy. Some investigators recommend large doses, others, small. The treatment may be applied as a spray or locally.

Krebs and Bichel³²¹ advise that roentgen therapy be given according to the patient's symptoms and that the actual white cell count be disregarded. They state that each patient is an individual problem and should be treated accordingly. Merrill³²² reports 3 cases of leukemia in which uremia developed after roentgen therapy. In his opinion, uric acid metabolism should be carefully studied before and during treatment with roentgen rays to prevent this complication. The combination of transfusions and roentgen irradiation is considered by Corelli and Gaetano³²³ to be the most effective treatment. Popp and Watkins³²⁴ state that roentgen therapy is contraindicated in acute myelogenous leukemia, should be administered cautiously in aleukemic myelogenous leukemia and is beneficial in the chronic type.

Barnard and Ross³²⁵ gave large doses of sodium bicarbonate to 2 patients with myelogenous leukemia. They continued the therapy until alkalosis developed. No changes in the hemogram were observed, a result which the authors offer as evidence that neoplastic growth is not related to alkalosis of the tissues.

The phosphorus metabolism of normal and leukemic mice was studied with the aid of radioactive phosphorus by Lawrence and his co-workers³²⁶. Leukemia was produced in the rats by the injection of malignant cells. The average uptake of phosphorus per gram of whole body weight by bone was only slightly greater in leukemic animals than in normal ones, while the uptake of phosphorus by muscle was slightly less in leukemic than in normal animals. The uptake and exchange of phosphorus in the spleen and lymph nodes were strikingly greater in leukemic animals than in normal ones, although the total phosphorus content of leukemic mice and that of normal mice are approximately the same. In view of these results, as well as the fact that the beta rays

321 Krebs, C, and Bichel, J. Directions for Roentgenotherapy of Leukoses, *Ugeskrift for læger* **102** 349, 1940.

322 Merrill, D. Uremia Following X-Ray Therapy in Leukemia, *New England J. Med.* **222** 94, 1940.

323 Corelli, F, and Gaetano, M. Vantaggi delle ripetute modiche transfusioni di sangue nella cura delle leucemie, *Riforma med.* **56** 167, 1940.

324 Popp, W. C, and Watkins, C. H. Hematologic Diagnosis and Roentgenologic Treatment of Myelogenous Leukemia, *Radiology* **34** 663, 1940.

325 Barnard, R. D, and Ross, P. W. The Effect of Alkalosis on the Blood Picture in Chronic Splenomyelogenous Leucemia, *J. Lab. & Clin. Med.* **25** 345, 1940.

326 Lawrence, J. H, Tuttle, L. W, Scott, K. G, and Connor, C. L. Studies on Neoplasms with Aid of Radioactive Phosphorus. I. The Total Phosphorus Metabolism of Normal and Leukemic Mice, *J. Clin. Investigation* **19** 267, 1940.

penetrate only about 1 cm, the authors conclude that radioactive phosphorus may be a good therapeutic agent for treating leukemia

Lawrence³²⁷ reported 5 cases of leukemia and 2 cases of polycythemia treated by radioactive phosphorus. The substance was administered orally as sodium phosphate in amounts less than a cathartic dose. Conclusions as to the results cannot be drawn, as too few facts are known. It may be said, however, that radioactive substances have the advantage of irradiating the entire body without producing reactions. Warren,³²⁸ also, has used radioactive phosphorus as a therapeutic agent, in 4 cases of leukemia.

Experimental leukemia has added considerable information to the scanty knowledge of this disease. Burchenal³²⁹ studied the relationship of pregnancy to leukemia. Pregnant mice were given intravenous injections of 0.1 cc. of a cell suspension from the spleen of a leukemic mouse. Eighteen females died with leukemia and bore 114 young, 7 mice died with the fetuses in utero, 6 died post partum and lost their young, and the young of 5 other mice that died post partum were raised by foster mothers. In all instances, the fetuses were normal. The offspring died when given injections of a cell suspension from the spleen of a leukemic mouse. The author concludes that mice do not transmit leukemia, that the offspring of leukemic mothers have no immunity and that since the disease did not pass through the placenta, it is not caused by a virus. To substantiate his results, Burchenal cites the literature and states that there is no authentic case in which leukemia was transmitted to the fetus from the mother.

Furth, Barnes and Brower³³⁰ investigated the resistance to transmissible leukemia in mice by means of parabiosis. Three strains of mice were used. Animals of the same sex were joined by suturing the peritoneum, muscles, skin and scapulas. The following experimental combinations were employed: (1) 2 mice susceptible to leukemia (only 1 inoculated), (2) 1 susceptible and 1 resistant mouse (the former inoculated), (3) 1 susceptible and 1 resistant mouse (the latter inoculated), and (4) 1 susceptible and 1 partially resistant mouse (either inoculated). In the first experiment both animals died of leukemia.

327 Lawrence, J. H. Nuclear Physics and Therapy. Preliminary Report on a New Method for Treatment of Leukemia and Polycythemia, *Radiology* **35** 51, 1940.

328 Warren, S. The Treatment of Leukemia by Radio-Active Phosphorus, *New England J. Med.* **223** 751, 1940.

329 Burchenal, J. H. Experimental Studies on Relation of Pregnancy to Leukemia, *Am. J. Cancer* **39** 309, 1940.

330 Furth, O. B., Barnes, W. A., and Brower, A. B. Studies on Resistance to Transmissible Leukemia in Mice by Means of Parabiosis, *Arch. Path.* **29** 163 (Feb.) 1940.

about the same time and at practically the same stage of the disease. In the second experiment the susceptible mouse died of leukemia, but the resistant animal did not contract the disease. The same results occurred in the third experiment except that the susceptible animal had a delayed death. In the last experiment, when the partially resistant mouse was inoculated, the nonresistant animal always died and occasionally the partially resistant one did, when the susceptible animal was inoculated, it always died, but in only 1 case did a partially resistant mouse die. As a result of these experiments, the investigators reached the following conclusions: 1. Leukemic cells pass from one susceptible parabiont to the other and produce leukemia in both. 2. The development of leukemia in a susceptible mouse inoculated with leukemic cells is not influenced by its parabiotic union with a resistant mouse, and, further, leukemic cells injected into a resistant mouse may pass to a susceptible parabiont, producing leukemia in the latter without affecting the former. 3. Resistance to transmissible leukemia in mice of a stock only partially resistant to leukemia remains unaltered by parabiosis with susceptible mice. 4. Since the presence of blood vascular anastomosis between parabionts has been demonstrated by the passage of red blood cells and agglutinins from one to the other and since the course of the disease has not been altered it would appear that transfusions are useless.

BONE MARROW

The importance of studies of the bone marrow as an aid in hematologic diagnosis can no longer be denied. However, many problems related to methods of obtaining marrow to terminology and to interpretation still exist. Gordon³³¹ compares the advantages and disadvantages of sternal aspiration and trephining. The former method is rapid, is almost painless and can be repeated often. However, many cells are traumatized, few immature cells are dislodged, there is loss of topographic relationship and an admixture of marrow with peripheral blood occurs. By the trephine method more material can be obtained, the histologic relationship of cells and stroma is preserved and the most immature cells are obtained. The disadvantages of this procedure are that an operating permit is necessary, an open incision is required, the procedure is extremely painful and often it is difficult to identify the cells.

According to Gordon, bone marrow studies are indicated as an aid in the diagnosis of obscure conditions, as a corroborative diagnostic procedure, as a help in the determination of the prognosis and the understanding of the pathogenesis of disease and as a method for the bioassay of specific hematologic agents.

³³¹ Gordon H. Sternal Marrow Biopsy. Methods, Indications and Limitations, Kentucky M J 38 170, 1940

Wilson ³³² is more or less in agreement with the aforementioned advantages and disadvantages and in addition, states that in obtaining specimens for biopsy there is the risk of infection and hemorrhage

Bone marrow obtained from 58 autopsy specimens was studied by Jeanneret ³³³ The author points out that if the material is obtained within one hour after death it is comparable to living marrow The polymorphonuclear leukocytes degenerate first and are followed by the myelocytes The nuclei of the normoblasts undergo pyknosis and fragmentation Plasma cells, lymphocytes, eosinophils and stroma cells change slowly Mitotic figures and thrombocytes disappear in one to two hours The percentage of myeloid cells falls to zero in eight to twenty-four hours Septic conditions have a noticeable effect on the bone marrow pattern The author believes that sections of bone marrow are better than aspiration specimens, since the former contain more immature cells and the relationships of their tissues are preserved

McLean ³³⁴ performed sternal puncture on 120 patients with various types of blood dyscrasias According to his normal standards, the ratio of white blood cells to red blood cells is 6:1 If the mature white cells are omitted, however, the ratio (leukoerythrocytic ratio) is reduced to 1:4 In pernicious anemia in relapse, the marrow is hyperplastic and megaloblastic, in remission megaloblasts persist but are decreased in number McLean states that sternal punctures are of no value in the diagnosis of microcytic anemia and are unnecessary in the recognition of leukemia, since the marrow picture is similar to that of the peripheral blood He further adds that in atypical cases, if other methods fail, sternal aspiration is indicated

Hyperplastic normoblastic erythropoiesis was observed by Nordenson ³³⁵ in cases of pernicious anemia in remission, of hypochromic anemia, of hemolytic jaundice, of erythroblastosis in children, of hemorrhage, of toxic anemia and of anemia associated with digestive disorders The author points out that degenerative myelopoiesis is diagnostic of pernicious anemia, although megaloblasts may be absent, that lymphatic metaplasia is pathognomonic of lymphadenosis and that increased numbers of megakaryocytes occur in polycythemia and in essential thrombopenic purpura Monocytic leukemia is characterized by an increase of monocytes in the bone marrow In myeloma there is a hyperplasia of plasma cells Typical cells of Gaucher's disease, Niemann-Pick disease and Schuller-Christian disease may be observed in the marrow in cases

332 Wilson, T. E. Sternal Biopsy, *M. J. Australia* **1** 405, 1940

333 Jeanneret, H. La moelle osseuse en clinique et a la salle d'autopsie. Étude comparative, *Schweiz. med. Wchnschr.* **70** 351, 1940

334 McLean, J. A. Sternal Puncture, *M. J. Australia* **2** 395, 1940

335 Nordenson, N. G. Sternal Puncture and Its Practical Diagnostic and Theoretical Significance, *Nord. med. (Hygiea)* **6** 834, 1940

of these conditions Nordenson also used the aspiration method to study the embryonic development of the various types of blood cells

The bone marrow in sarcoidosis is described by Lucia and Aggeler³³⁶ They found that the reactions of the bone marrow were similar to those associated with chronic infection Lınarzi and Schleicher²¹⁰ studied the marrow of patients with various types of purpura and hemorrhage In essential purpura (active phase) the bone marrow showed an increase in the number of megakaryocytes and the presence of many young cells After splenectomy the bone marrow returned to normal Hyperplasia of the megakaryocytic tissue was more noticeable in chronic purpura than in the acute form of the disease In patients with thrombopenic purpura who continued to bleed after splenectomy, the bone marrow appeared abnormal The marrow in symptomatic purpura was characterized by an increase in megakaryocytes, which was less marked than in the other types of purpura After hemorrhage intermediary megakaryocytes predominated The authors conclude that the decreased number of platelets present in the peripheral blood in essential purpura is due to arrested maturation of the megakaryocytes

Observations on the human sternal bone marrow in cases of hyperthyroid and myxedematous states are reported by Jones³³⁷ Nucleated cells were increased in conditions of hyperthyroidism and after thyroid therapy in myxedema In hypothyroidism the number of nucleated cells was decreased as compared with the normal After thyroidectomy the bone marrow returned to normal In the author's opinion, the hyperplasia is myeloid in character and is not reflected in the peripheral blood

Israels³³⁸ recommends the study of the bone marrow in atypical cases of leukemia Lymphocytosis, which is characteristic of leukemia, may also be seen in infectious mononucleosis and in aplastic anemia In glandular fever all the other elements of the bone marrow are normal, in aplastic anemia the lymphocytosis is relative and the other cells are normal Thus the diseases can be easily differentiated The bone marrow in infectious mononucleosis was also studied by Leitner³³⁹ The marrow revealed a myelocytic reaction, with interference of cell maturation due to splenic hyperfunction In the author's opinion, this

336 Lucia, S. P., and Aggeler, P. M. Sarcoidosis (Boeck), Lymphogranulomatosis Benigna (Schaumann), Observations on the Bone Marrow Obtained by Sternal Puncture, *Acta med Scandinav* **104** 351, 1940

337 Jones, R. M. Human Sternal Bone Marrow in Hyperthyroid and Myxedematous States, *Am J M Sc* **200** 211, 1940

338 Israels, M. C. G. Lymphatic Leukaemia The Value of Sternal Puncture in the Diagnosis of Atypical Cases, *Brit M J* **2** 1132, 1939

339 Leitner, S. J. Das lymphoide Drüsengewebe (Mononucleosis Infectiosa) mit besonderer Berücksichtigung des Sternalmark-befundes, *Schweiz med Wchnschr* **70** 117 1940

hyperfunction accounts for the leukopenia which often occurs in infectious mononucleosis

The bone marrow in 6 additional cases of achrestic anemia is described by Israels and Wilkinson³⁴⁰ They state that the bone marrow simulates that of pernicious anemia They add that true megaloblasts do not occur in aplastic anemia, hence the two diseases can be easily differentiated Morrison and Samwick³⁴¹ report a case of aplastic anemia treated by sternal transfusions In their opinion, the bone marrow was given not as a transplant but because it contains some substance necessary for bone marrow growth The bone marrow in a case of benzene poisoning was studied by Gray and his co-workers³⁴² All the normal elements were reduced

The presence of an increased number of plasma cells in the bone marrow of patients with multiple myeloma was observed by Haden and Rumsey³⁴³ and King³⁴⁴ The bone marrow of patients with various diseases producing myelophthisic anemia was studied by Mettier³⁴⁵ and by Thompson and Illyne³⁴⁶ Tumor cells were observed by Kreyberg and Poppe³⁴⁷ in the marrow of 8 patients with various types of malignant disease In their opinion, biopsy sections give more information than sternal aspirations

According to Ling and his colleagues,³⁴⁸ culture of the bone marrow is a simple, rational and reliable method for diagnosing typhoid and paratyphoid fever In a series of 38 cases, cultures of the marrow, blood, urine and stools were made simultaneously Bone marrow cultures

340 Israels, M C G, and Wilkinson, J F New Observations on the Aetiology and Prognosis of Achrestic Anaemia, *Quart J Med* **9** 163, 1940

341 Morrison, M, and Samwick, A A Intramedullary (Sternal) Transfusion of Human Bone Marrow Preliminary Report, *J A M A* **115** 1708 (Nov 16) 1940

342 Gray, I, Greenfield, I, and Lederer, M Benzene Poisoning Report of Case with Sternal Marrow Studies, Autohemagglutination and Autopsy, *J A M A* **114** 1325 (April 6) 1940

343 Haden, R L, and Rumsey, J M Multiple Myeloma, or Myelomatosis, *M Clin North America* **24** 369, 1940

344 King, B B Solitary Plasma Cell Myeloma of Bone as an Initial Stage of Multiple Myeloma, *J A M A* **115** 36 (July 6) 1940

345 Mettier, S R Hematologic Aspects of Space Consuming Lesions of the Bone Marrow (Myelophthisic Anemia), *Ann Int Med* **14** 436, 1940

346 Thompson, W P, and Illyne, C A The Clinical and Hematologic Picture Resulting from Bone Marrow Replacement, *M Clin North America* **24** 841, 1940

347 Kreyberg, L, and Poppe, E Tumor Cells in Sternal Bone Marrow, *Lancet* **1** 593, 1940

348 Ling, C C, Taur, S S, Hsueh, P C, and Yang, S Y Medulloculture in the Diagnosis of Typhoid and Paratyphoid Fevers Analysis of Thirty-Eight Cases, *Chinese M J* **57** 11, 1940

gave the highest percentage of growths during the early and late stages of the disease, and often during convalescence. The growth appeared more rapid and luxuriant in these cultures. In the authors' opinion, it is easier to obtain bone marrow than blood, and therefore culture of the marrow should be routinely employed.

Osgood³⁴⁹ gives an excellent résumé of his method of culture of human marrow. By this procedure, he was able to study the various effects produced by roentgen rays on marrow cells. From his observations, he suggests that the roentgen rays inhibit mitotic and amitotic division and the cells disappear gradually as they mature and live out their natural life span. Bullowa and his colleagues,³⁵⁰ employing Osgood's technique, studied the effect of sulfapyridine alone and with serum on pneumococcic pneumonia and on pneumococcus-infected marrow cultures. In marrow cultures, sulfapyridine in a concentration of 5 mg or more per hundred cubic centimeters leads to ultimate sterility with inoculums of 500 or less per cubic centimeter of types I, II, III or V pneumococci, however, controls uniformly grow out to number over 100,000,000 colonies per cubic centimeter. The larger the initial inoculum, the less likely sulfapyridine will lead to sterility. Sulfapyridine was more effective than sulfanilamide. Specific antiserum appeared to increase the effectiveness of sulfapyridine, although occasionally the reverse occurred. Within definite ranges the higher concentrations of the drug are more effective. Fresher strains of the bacteria are more resistant, and all organisms are not rapidly killed by the drug. In proper doses the drug does not injure the marrow cells, nor does it increase or decrease phagocytosis. The organisms retain their capsule and specificity but often become distorted. Acetyl sulfapyridine is ineffective. Serum from untreated patients with pneumonia is not bactericidal, serum from treated patients has bactericidal properties proportional to the sulfapyridine and antibody content. Administration of the drug alone is followed by a lower death rate than employment of serum alone or of a combination of the two. The lowest mortality rate occurred in cases in which serum and the drug were used in combination in treating the early stages of the disease.

In a similar experiment, Osgood³⁵¹ noted the effectiveness of neoarsphenamine, sulfanilamide and sulfapyridine in marrow cultures.

349 Osgood, E. E. Culture of Human Marrow. Summary of Studies to Date, *West J. Surg.* **48** 540, 1940.

350 Bullowa, J. G. M., Osgood, E. E., Bukantz, S. C., and Brownlee, I. E. Effect of Sulfapyridine Alone and with Serum on Pneumococcic Pneumonia and on Pneumococcus-Infected Marrow Cultures, *Am. J. M. Sc.* **199** 364, 1940.

351 Osgood, E. E. Effectiveness of Neoarsphenamine, Sulfanilamide, Sulfapyridine in Marrow Cultures with Staphylococci and Alpha Streptococci, *Proc. Soc. Exper. Biol. & Med.* **42** 795, 1939.

inoculated with staphylococci and alpha streptococci. Neoarsphenamine in a concentration of 3 to 9 parts per million was more effective than a 1:10,000 concentration of either sulfanilamide or sulfapyridine and did not significantly damage the marrow cells. The toxic and therapeutic responses of the blood and bone marrow to sulfanilamide were observed by Paul and Limarzi.³⁵² Nine patients were given 24 to 72.3 Gm of the drug over a period of eight to seventeen days. Macrocytic anemia was often produced and was accompanied by a normoblastic reaction of the bone marrow. When acute hemolytic anemia occurred, the bone marrow exhibited a more marked reaction, with the presence of younger cells.

Israels,³⁵³ employing a modified technic of Osgood, cultured bone marrow and studied the development of individual strains of white cells. The granulocytes, reproduced by mitosis, had differentiating granules, and their nuclei showed lobulation. Lymphocytes exhibited amitotic division. The monocytes developed into phagocytic cells, and the early forms showed active mitosis.

Higgins and Machella¹⁰² administered sulfanilamide to rats and killed them at various intervals. The effects of the drug on the bone marrow were studied. On the fourth day, a marked myeloid and a mild erythroid stimulation were noted. On the sixth day, if anemia was present, the erythroid stimulation predominated, and this condition persisted after the sixth day regardless of the appearance of anemia. The investigators concluded that the alterations of the leukocytes in the peripheral blood were probably due to nuclear changes produced in the immature white cells in the bone marrow.

352 Paul, J. T., and Limarzi, L. R. Toxic and Therapeutic Response of Blood and Bone Marrow to Sulfanilamide, *Proc. Soc. Exper. Biol. & Med.* **43**: 29, 1940.

353 Israels, M. C. G. The Culture in Vitro of Leucocytes from Human Bone Marrow, *J. Path. & Bact.* **50**: 145, 1940.

Book Reviews

The Endocrine Function of Iodine By William Thomas Salter Price, \$3.50
Pp 351, with 40 illustrations Cambridge, Mass Harvard University Press,
1940

In this monograph the function of iodine in the endocrine system is correlated with the involved chemical, pathologic and experimental and clinical physiologic aspects. A selective, rather than exhaustive, consideration of the literature on thyroid activity comprises the major part of the book. Using iodine as the common denominator, the author makes an orderly approach to a mass of unorganized data and thereby attains a clearcut statement of clinical and experimental progress in the field.

Considering the author's background, it is neither unexpected nor unwarranted that considerable space is devoted to the special properties and development of knowledge of thyroglobulin. The thyroid-pituitary relationships are considered extensively. Recent advances in determinations of iodine in the blood, including the differentiation of the organic and inorganic forms, are evaluated and discussed. The treatment of the role of the hypothalamus serves to demonstrate the author's liberal approach to the subject of iodine metabolism. In this respect the chapter on iodine and the ovary should be mentioned. The important work being done on iodine balance is reviewed comprehensively. Recent work with radioactive iodine is critically surveyed and interpreted. This presentation is especially provocative to thought, as it tends to supplement and expand the preceding background of the relation of iodine to the physiologic activities of the thyroid gland. A short concluding chapter on clinical problems of thyroid disease is not sufficient to recommend the book for strictly clinical reading. An appendix contains brief statements of methods of chemical and biologic assay and miscellaneous information of interest to the student of thyroid problems. The foregoing factors, along with the excellent cross-indexed bibliography, the complete index and the contemporary data, give the volume the aspect of a handbook on thyroid lore.

The book should prove to be of special value to the student and the investigator of the physiologic relations and the diseases of the thyroid gland, it should aid greatly in orienting the reader to the mass of data produced in this important field of endocrinology in the last ten years, the thoughtful clinician should find it highly stimulating. Lastly, the author demonstrates a new technic in the analysis of an endocrinologic problem.

Obesity and Leanness By Hugo R. Rony, M.D. Price, \$3.75 Pp 300, with
32 engravings Philadelphia Lea & Febiger, 1940

The increased attention paid to obesity as an important factor in the etiologic and pathogenic relations of many pathologic conditions makes this book particularly appropriate at this time. Much less attention has been paid to leanness, but in this monograph Rony has attempted, successfully, incidentally, to show systematically that these two abnormal conditions of the body are "facets of a single problem."

The first section of the book, some 210 pages, is divided into two parts, the first having to do with the physiologic relations of fats and fatty tissue and the second with the pathogenesis of obesity and of leanness. In this particular section the author deals with the role that is played by caloric intake and output, by the endocrine system and by the nervous system. In the first portion, so far as caloric intake is concerned, he stresses the fact that most fat people have abnormal appetites, whereas the opposite is true of lean persons. He calls attention to the influence of heredity and to the important consideration of body build.

The second section, part III of the book, deals with the clinical aspects of obesity and leanness. These 82 pages include a discussion of the classification and the diagnosis of obesity and of leanness, the clinicopathologic aspects of obesity and the therapy of the two conditions. It was to be expected that in the treatment of obesity the author would condemn the use of dimtrophénol. On the other hand, many pages are devoted to the administration of thyroid, but here also caution is indicated in the use of this drug, as shown by the listing of some eight important contraindications to its use.

While Rony has written primarily for the physician with a good medical education, in the first section of the monograph he lays for the man who is in general practice but is not necessarily trained in any special field a foundation which will permit him to follow intelligently all that comes later. This will make the book available to a large group of readers. Well illustrated, with excellent format, the monograph maintains the high publishing standards which one expects from the company that has brought out the book.

Dermatologic Allergy. By M. B. Sulzberger, M.D., Assistant Clinical Professor of Dermatology and Syphilology, Columbia University College of Physicians and Surgeons. Price, \$8.50. Pp. XXII + 540, with 39 illustrations and 13 color plates. Springfield, Ill., and Baltimore: Charles C. Thomas, Publisher, 1940.

In the preface to his book the author makes the following statement: "This is not intended to be a book of reference, an encyclopedic treatise on allergy or dermatologic allergy. My objective has not been a presentation for the expert, for the immunologist, the allergist or the dermatologist who is well acquainted with this subject, this book is intended to be only a primer, an introduction to dermatologic allergy, in the form of lectures based on those I have been giving to beginners."

The volume is rather more than the author promises. There are fourteen chapters. Each one represents a well organized lecture and deals with a single phase of a complicated subject. The writing is as simple as possible, particularly clear are the definitions of terms used and the descriptions of technics to be employed. A few select bibliographic references are given at the end of each lecture to whet one's appetite for more knowledge. The illustrations are admirable.

At the end is an interesting appendix, wherein is printed a translation of von Pirquet's article which first made use of the term "allergy." Here, too, are a list of accredited substances useful for patch tests and a short discussion of the proper management of urticarial and eczematous dermatoses.

On the whole, this is an unusually useful primer, if so pretentious a monument of work can be thus regarded. Many students will use it for reference and will consider it as a valuable encyclopedic treatise on dermatologic allergy.

Pharmacology and Therapeutics. By Arthur R. Cushny, M.D., LL.D., F.R.S., late Professor of Materia Medica and Pharmacology in the University of Edinburgh, thoroughly revised by C. W. Edmunds, M.D., Professor of Materia Medica and Therapeutics in the University of Michigan, Ann Arbor, Mich., and J. A. Gunn, M.D., D.Sc., F.R.C.P., Professor of Pharmacology in the University of Oxford, Oxford, England. Twelfth edition. Price, \$6.50, cloth. Pp. 952, illustrated, with 66 engravings. Philadelphia: Lea & Febiger, 1940.

The changes in the twelfth edition of this established text consist primarily in the addition of approximately 50 pages of material concerning new therapeutic agents (sulfanilamide, hormones, vitamins) which have been developed in the four years that have elapsed since the eleventh edition. Complete alteration of the older subject matter has not been attempted, although minor changes have been made. The sketchiness with which some subjects are treated is explained in the prefacial statement, as well as by the further generalization that the constant increase in the scientifically recognized materia medica makes it difficult to combine the

essentials of both experimental pharmacology and therapeutics in 900 pages. Certain "textbook errors" are perpetuated, especially those regarding the actions of drugs on man, errors originally arising from some unwarranted transfer of evidence from experiments on a single animal species.

Considered in its entirety the volume is a good text, the revision reasonably satisfactory and the statements regarding drug action as critical as is to be expected from authors who cannot assume claim to first hand knowledge of all phases of a complicated field.

Magenphysiologie fur Rontgenzwecke By Dr. Med. Habil. G. A. Weltz
Price, 12 marks. Pp. 76, with 62 plates. Leipzig: Georg Thieme, 1940.

In this monograph on the physiology of the stomach, the author presents a series of hypotheses on the function of the stomach. The book is divided into four parts. The first chapter deals with the fundamental laws governing tone and peristalsis. The author enumerates them as follows:

1. Tone is independent of peristalsis. Peristalsis, however, is a function of tone.

2. Peristalsis has a stimulus threshold.

3. The stimulus threshold of peristalsis is dependent on the degree of tone and the increase of pressure.

The second chapter is devoted entirely to tone, the third, to peristalsis and the fourth, to emptying.

The hypotheses are proved by animal experimentation as well as clinical roentgenologic studies. The author makes good use of roentgen kymography. The monograph includes a neat device which enables the reader to restore motion to the kymographic illustrations.

In the preface Dr. Weltz expresses the hope that he will provide a stimulus for further research in normal and abnormal gastric physiology. I believe he has ably succeeded. This book is worthy of careful study by the pure physiologist as well as the roentgenologist.

Diseases of the Digestive System By Eugene Rosenthal, M.D. Price, \$8.50
Pp. 394, with 234 illustrations. St. Louis: The C. V. Mosby Company, 1940.

This book is the most profusely illustrated medical text that the reviewer has yet seen. The author states that by the use of the many labeled and multicolored diagrams the student is enabled to obtain an association of ideas in every case. There is no question that the use of these illustrations will be a great help to those persons who have a good visual memory. Most of the diagrams are simple and quickly understood, while others, such as the one on page 347, are more intricate.

The discussion of the various diseases is done in an orderly and fairly complete manner, although in some instances, the dysenteries, for example, the handling is sketchy.

In dealing with therapy, the author employs freely the proprietary names of various drugs which are not generally used in this country. There is, among other things, no reference to vitamin K in the discussion of the treatment of obstructive jaundice, and the use of the Miller-Abbott tube in cases of intestinal obstruction is not mentioned.

The book, because of its novel arrangement, is interesting to read, the printing is excellent and the binding is good.

Manual of Medical and Surgical Emergencies Edited by J. C. Geiger, M.D.,
Director, Department of Public Health, City and County of San Francisco.
Price, \$2.50. Pp. X + 199. San Francisco: J. W. Stacey, Inc., 1940.

Not long ago a farmer in the western part of California wrote to the medical school for advice. It appeared that rattlesnakes were invading his territory and he wished to know what to do if any of his people were bitten. He said that the doctors in his part of the world appeared to know peculiarly little of such matters.

This manual will be useful to all physicians who are forced to meet medical emergencies of any sort. It has been compiled by a group of experts who know of what they write. It is well indexed and is written so simply and clearly that when a sudden juncture demanding immediate medical action occurs, this manual can be pulled from the shelf and referred to, and by its advice, without delay, can make possible intelligent, expert management.

The subject matter included in the book covers a wide range of possibilities from the care of abdominal emergencies through the entire alphabet of accidents, down to how to treat wounds from a wringer or x-ray burns. Every hospital library should have copies at hand which the interns can get at, even the specialist serenely at work in his office may be glad of a copy in his library when the Black Widow caresses him.

A Textbook of Medicine By American authors. Edited by Russell L. Cecil. Fifth edition. Price, \$9.50. Pp 1744, with 173 illustrations. Philadelphia and London: W. B. Saunders Company, 1940.

The new fifth edition of Cecil's "Textbook of Medicine" seems to establish the book definitely as one of the institutions of American medicine. Compressed into relatively brief space one finds a miniature system with concise but authoritative articles by men whose names for the most part are outstanding in their fields. It would take too much space to discuss individual sections, but the editor is to be congratulated on the character of the present revision, in which a good many articles have been entirely rewritten, sometimes by a new man. While a book of this sort lacks in a sense the homogeneous viewpoint of a single writer, it must be admitted, even if with regret, that no one man can any longer cover the subject with authority. The reviewer finds himself constantly using Cecil for rapid reference, and usually with satisfaction.

Annual Review of Physiology By J. Murray Luck and Victor E. Hall. Vol. II. Price, \$5. Pp 501. Stanford University Press, Calif. American Physiological Society and Annual Reviews, Inc., 1940.

In volume II of the "Annual Review of Physiology" the tradition so well established by volume I is continued. The twenty reviews cover, among other things, such important subjects as peripheral circulation, the heart, endocrine glands, special senses and blood. As in last year's volume, the material is tremendously condensed and really furnishes a key to the large bibliographies which follow each article. Every physician who wishes to keep up with the role of physiology in medicine needs this book.

Organismen und Umwelt By R. Otto, K. Felix and F. Linke. Price, 15 marks. Pp 275, with 67 illustrations. Dresden and Leipzig: Theodor Steinkopff, 1939.

This paper-bound volume contains the transactions of the second scientific conference held at Frankfurt on the Main, Germany, in June 1939. It is composed of twenty papers which deal with a great variety of subjects in the field of medicine and allied sciences. Most of the papers are supplemented by discussions. Since the contributors come from many European nations, this volume gives one an interesting insight into continental thought on these subjects.

Food, Nutrition and Health By E. V. McCollum and J. E. Becker. Price, \$1.50. Pp 127. Baltimore: The Lord Baltimore Press, 1940.

This little book, written by seasoned authorities in the field, gives in a small space a great amount of information about food and vitamins. After discussing the needs of the normal diet, the authors present interesting chapters on the relation of diet to the teeth, to pregnancy and the like. The reviewer has only one minor criticism. At times the discussion is a little too deep for the average layman.

Die Geschichte der Schwindsucht By Dr Richard Bochall Price, 4 30 marks Pp 73 Leipzig Georg Thieme, 1940

This booklet of 73 pages deals with what was called phthisis before the time of Bichat, and it is evident that the term includes tuberculosis of the lungs, to the history of which a second volume will be devoted

The author does not avoid the danger of overemphasizing the merits of our great medical forebears, particularly in the field of therapy This is a rather prevalent error in such treatises Another individual error is the author's reference to passive motion when a patient is carried in a chair or other conveyance It is perfectly true that this is passive motion, but it is not the kind of passive motion generally understood in medicine

Even if the author does not seem a profound student or always a clear thinker, the monograph may be perused with some profit

Complete Guide for the Deafened By A F Niemoeller Price, \$3 Pp 256 New York The Harvest House, 1940

Handbook of Hearing Aids By A F Niemoeller Price, \$3 Pp 156 New York The Harvest House, 1940

These two little books seem to the reviewer who is not an expert in the subjects involved to cover them adequately and in an interesting way In the guide for the deafened the short chapters dealing concisely with every phase of deafness, including lip reading and the psychologic problems of the hard of hearing, seem especially useful

Psychotherapy By Lewellys F Barker Price, \$2 Pp 218 New York D Appleton-Century, 1940

Most physicians reading psychiatric literature soon become lost in a morass of terminology and are unable to make much sense out of the technical material Dr Barker's little book gives to the reader not specially trained in psychiatry a concise and stimulating account of the methods and results of dealing with the common psychoneuroses encountered by the physician in general practice The authoritative touch is evident throughout, probably no one in the country has better results in practice with the neurotic patient than does Dr Barker An interesting bibliography is appended

Diseases Transmitted from Animals to Man By Thomas G Hull Second edition Price, \$5 50 Pp 403, with 45 illustrations and 55 tables Springfield Ill Charles C Thomas, Publisher, 1941

It is an interesting sidelight on modern specialization that the editor of this book, which deals with only a part of the field of infection, felt the need of no less than fourteen collaborators It is the good fortune of the reader, however, to gain the authoritative discussions of these experts All the important diseases which may be transmitted to man from animals are described Most of the articles stress epidemiologic aspects, and in some cases the clinical descriptions are perhaps too brief, for instance that of botulism The recently developed prophylaxis of tetanus by toxoid is also barely mentioned Such few shortcomings are, however, more than balanced by the general high quality of the book, the excellent illustrations, the instructive diagrams and the attractive format

The 1940 Year Book of Pathology and Immunology By Howard T Karsner and Santoid B Hooker Price, \$3 Pp 688, with 115 illustrations Chicago The Year Book Publishers, 1940

The Year Book Series has been so successful that the idea of a volume on pathology and immunology seems in order Under the editorship of Dr Karsner and Dr Hooker a most attractive volume has been produced The material does not lend itself to review because it is a series of abstracts of articles, but here in compact form one finds boiled down several hundred of the most important contributions of the year The volume should be of great use to pathologists, to bacteriologists and to physicians in general

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